3 Consultative hematology 2: women's health issues

Leslie Skeith, Molly Weidner Mandernach, and Andra H. James

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Hematologic health issues in women with blood disorders: the multidisciplinary team

The diagnosis and management of women's health issues in hematology requires a multidisciplinary approach involving some combination of hematologists, internists, family practice physicians, obstetrician-gynecologists, pediatricians, surgeons, anesthesiologists, and other health care providers. Because women and girls with blood disorders may be at greater risk for bleeding, thrombosis, and reproductive pregnancy complications, their care requires a team of experts with the availability of specialized laboratory, pharmacy, and blood bank support. During pregnancy, this team should also include a maternal fetal medicine (MFM) specialist, because in many academic centers it is the MFM group that consults the hematologist, and some of these patients require shared care between MFM and hematology.

This chapter summarizes the most recent available evidence and guidelines to minimize risk in women with blood disorders.

Hematologic health issues in pregnant women: anemia and thrombocytopenia

During pregnancy, the most common hematologic conditions are anemia and thrombocytopenia.

Anemia in pregnancy: what the hematologist needs to know

- Iron deficiency anemia is the second most common cause of anemia in pregnancy and may be treated with oral iron supplementation or intravenous (IV) iron (sucrose or sodium ferric gluconate) after 13 weeks of gestation.
- A minimum of 400 μg of folic acid daily is recommended for pregnant women.
- In women with underlying hemolytic disorders, folic acid (4 to 5 mg daily) is recommended.
- Microangiopathic hemolytic anemias are characterized by nonimmune intravascular hemolysis and include thrombotic thrombocytopenic purpura (TTP); complement-mediated thrombotic microangiopathy (TMA); and

Conflict-of-interest disclosure: Andra H. James: Research funding: Coagulant Therapeutices; Consulting: Cerus, Octapharma, Tremeau, Hemosonics, Coagulant Therapeutics; Leslie Skeith: Research funding: CSL Behring; Honoraria: Leo Pharma, Sanofi.

Off-label drug use: Almost all medications are considered off-label in pregnancy.

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hemolysis, elevated liver function tests, and low platelets (HELLP) syndrome. Review of the peripheral blood smear is instrumental in the evaluation particularly when both anemia and thrombocytopenia are present.

- Pregnancy in women with sickle cell disease (SCD) is associated with increased maternal and fetal morbidity and mortality. Acute pain episodes are more frequent and affected women may require transfusion therapy. Aspirin (81 mg) is also recommended.

During normal pregnancy, a physiologic expansion of plasma volume begins in the first trimester and continues through the third trimester. The increase in plasma volume is greater than the increase in production of red blood cells, resulting in physiologic or dilutional anemia, which is the most common cause of anemia in pregnancy. Current guidelines suggest anemia is defined as hemoglobin (<11 g/dL in the first trimester, <10.5 g/dL in the second and third trimesters and <10 g/dL postpartum). Hemoglobin levels of <10 g/dL suggest the possibility of a pathologic process, such as nutritional deficiency. At present, there is no definitive evidence whether the hemoglobin threshold for transfusion should be <7 or <8 g/dL, although the increased fetal oxygenation needs entering the third trimester, the increased oxygenation needs of labor, and the risk of excess blood loss prompts most experts to raise the threshold to 8 g/dL in the third trimester, particularly for those patients who experience postpartum hemorrhage (PPH). On the other hand, transfusions increase the risk of red cell antigen sensitization and hemolytic disease of the newborn in subsequent pregnancies. Therefore, transfusion should be avoided when possible. The main determinant to transfuse should be the presence of active hemorrhage or hemodynamic compromise in addition to patient preference and symptoms.

Iron deficiency anemia

After physiologic anemia, iron deficiency is the second most common cause of anemia in pregnancy. The risk for iron deficiency anemia in pregnancy includes multiparity, short time intervals between pregnancies, poor nutritional status, and poor socioeconomic status. Iron requirements during pregnancy include 300 to 350 mg for the fetus and placenta, 500 mg for maternal red blood cell mass expansion, and 250 mg for anticipated blood loss during labor and delivery. The iron requirement increases from 0.8 mg per day in the first trimester to 7.5 mg per day in the third trimester; typically, absorption of iron from Western diets is approximately 1 to 5 mg per day. Thus, the Centers for Disease Control and Prevention (CDC) recommends all pregnant women receive an additional 30 mg of oral iron daily. Current guidelines also suggest that a serum ferritin level of <30 μg/L in pregnancy is consistent with iron deficiency.

If iron deficiency develops, current recommendations suggest pregnant patients receive 40 to 80 mg of elemental oral iron daily. Replacement should continue for 3 months and until at least 6 weeks postpartum, If hemoglobin is less than 7 g/dL, the patient has symptoms related to anemia, or gestational age is greater than 34 weeks, then referral to a hematologist for evaluation and administration of IV iron is appropriate. Failure to respond to oral iron after 2 to 3 weeks also warrants further management by a hematologist. IV iron may be considered after the first trimester.

Recommendations

For pregnant women, elemental iron (30 mg daily) is recommended. If anemia develops, administration daily or every other day is advised. For those not able to tolerate oral iron, parenteral iron after the 13th week is appropriate.

Megaloblastic anemia

Folate deficiency is the most common cause of megaloblastic anemia during pregnancy; however, both folate and cobalamin deficiency increase with advancing gestation. Vitamin B_{12} deficiency is rare but is seen more often in those who have undergone gastrectomy or have Crohn disease. A physiologic decline in vitamin B_{12} levels of 20% occurs in pregnancy but does not appear to be true deficiency as the metabolites homocysteine and methylmalonic acid are normal. Approximately 2.6 μg of vitamin B_{12} is required to support fetal neurologic development. Treatment of cobalamin deficiency in pregnancy is similar to that in the nonpregnant patient.

A minimum of 400 μg of folate daily is recommended from 2 months prior to pregnancy to 3 months postpartum, largely because of the importance of folate to neural tube development. Women who have increased demands for folate, including those with underlying hemolytic disorders, with folate metabolism disorders, or who are at increased risk of neural tube defects, should take 4 to 5 mg daily for the first trimester, then may take 400 μg daily.

Recommendations

For pregnant women, daily folic acid 400 μg is recommended. A higher dose of 4 to 5 mg, to begin 2 months before conception and continue through the first trimester (until closure of the neural tube), is recommended in women with hemolytic disorders or those at high risk of

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having offspring with neural tube defects. After the first trimester the dose may be decreased to 400 μg daily. Vitamin B_{12} deficiency should be treated similarly to vitamin B_{12} deficiency in the nonpregnant patient.

Aplastic anemia

Aplastic anemia is rare in pregnancy and may be either associated with or precipitated by pregnancy. The relationship, whether causal or secondary, between aplastic anemia and pregnancy is controversial. Cytopenias often progress during pregnancy and the disease may remit spontaneously after pregnancy.

Stem cell transplantation, which is the predominant therapy for nonpregnant aplastic anemia, is contraindicated in pregnancy. Women with preexisting aplastic anemia have a better prognosis than those with pregnancy-induced aplastic anemia, although the treatment is similar, including transfusion to maintain a platelet count >20,000/μL, growth factors (eg, granulocyte colony-stimulating factor) and, in select cases, immunosuppressive therapy after discussion with MFM. Antithymocyte globulin is not recommended. Among women who survive pregnancy-associated aplastic anemia, half may experience spontaneous remission, and the remainder are managed with antithymocyte globulin, immunosuppression, or stem cell transplantation.

Recommendations

For pregnant women with aplastic anemia, transfusions to maintain a hemoglobin of 7 to 8 g/dL, a platelet count of >20,000/μL (>50,000 for delivery and >70,000/μL for epidural), and growth factors (eg, granulocyte colony-stimulating factor), as needed, are recommended. In pregnancy-induced aplastic anemia, the role of termination or early delivery should be considered in management; case reports indicate improvement of aplastic anemia following pregnancy.

Autoimmune hemolytic anemias

Autoimmune hemolytic anemias are rare during pregnancy, with few reported cases. The newborn is at moderate risk for anemia. As in the nonpregnant patient, initial treatment with prednisone is recommended and, in refractory cases, splenectomy (in the second trimester) or immunosuppressive therapy (to be discussed in detail in the section on immune thrombocytopenic purpura [ITP]) can be considered.

Recommendations

Folic acid (4 to 5 mg) should be prescribed beginning 2 months preconception and continue until the end of the first trimester, then the dose can be reduced. Low-dose aspirin should be given for preeclampsia prevention. Immunosuppressive therapy can be considered.

Microangiopathic hemolytic anemias

Microangiopathic hemolytic anemias are disorders characterized by nonimmune intravascular hemolysis caused by abnormalities in the microvasculature or the presence of intravascular devices. In the thrombotic microangiopathies, hemolysis is caused by microthrombi in small capillaries and characterized by schistocytes, elevated lactate dehydrogenase (LDH) and indirect bilirubin, and reduced haptoglobin. Although they represent an uncommon cause of anemia in pregnancy (an estimated 0.6% to 1% of pregnancies are complicated by microangiopathies), they may have devastating consequences for both mother and child. These disorders, which include HELLP syndrome, TTP, and complement-mediated TMA, are challenging to diagnose, given the broad overlap in clinical presentation, and difficult to treat, given disparate therapies. These are discussed and recommendations provided in the "Thrombocytopenia in pregnancy" section that follows.

Hereditary anemias excluding sickle cell anemia

Hereditary spherocytosis is relatively common among patients of Northern European descent. Pregnancy may precipitate or worsen hemolytic crises, and maternal morbidity and fetal outcomes appear to be more favorable in previously prepartum splenectomized patients.

Regarding thalassemia, beta thalassemia minor and intermedia are associated with favorable outcomes, while beta thalassemia major can have a favorable outcome if the patient has normal cardiac function, has had transfusion therapy to maintain hemoglobin levels at 10 g/dL, does not have iron overload, and iron chelation therapy is stopped.

Recommendations

In both hereditary anemias, a higher than standard dose of folic acid (5 mg) should be prescribed beginning 2 months preconception and continue until the end of the first trimester, then the dose can be reduced. In beta thalassemia major, the hemoglobin level should be maintained at or near 10 g/dL and chelation therapy should be stopped.

Sickle cell disease

Pregnancy in women with sickle cell disease is associated with increased maternal and fetal morbidity and mortality caused by chronic hemolytic anemia and multiorgan dysfunction. The anemia of SCD impacts fetal growth, and vaso-occlusion and vasculopathy may impact placental

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health. Venous thromboembolism (VTE), intrauterine growth restriction, hypertensive disorders of pregnancy, preterm labor, and fetal loss are more common in women with SCD. Further, pain crises and other complications may worsen as red blood cell production frequently cannot keep up with oxygen demand.

There are unique aspects to the treatment of SCD in pregnancy. The recommended dose of folic acid is 4 to 5 mg daily. For women taking hydroxyurea, it is recommended to discontinue hydroxyurea before or at the time of conception and through the first trimester. Iron chelation therapy should be discontinued throughout pregnancy. Fetal risks of L-glutamine, voxelotor, and crizanlizumab are unknown at this time. Because of the increased prevalence of hypertensive disorders such as preeclampsia, pregnant women with SCD should be offered 81 mg of aspirin daily starting at 12 weeks of gestation and continuing for the duration of the pregnancy. Acute pain episodes occur in ~50% of pregnant women with SCD; thus, each woman requires an individualized pain plan. Because of the increased risk of VTE, patients who are not already being treated for VTE or who are not on VTE prophylaxis should receive VTE prophylaxis during hospitalizations and for the first 6 weeks postpartum.

Current guidelines suggest prophylactic transfusion is not routinely required for pregnant women with sickle cell disease; however, it should be considered for women previously using hydroxyurea for management of severe disease, multiple pregnancy, or previous or current medical, obstetric, or fetal problems related to SCD. Women on transfusions for stroke prevention should continue. Transfusion should be considered in women with worsening anemia or acute complications such as acute chest syndrome or acute stroke. Alloantibody screening should be performed early and phenotypic matching should be considered to avoid delayed hemolytic transfusion reactions or hemolytic disease of the newborn.

Recommendations

Consider prophylactic transfusion in select situations to include multiparity, a history of severe disease, or previous complications caused by SCD. Women receiving transfusions antenatally for stroke prevention should continue through pregnancy and those experiencing complications related to SCD, such as acute chest syndrome or stroke, should also receive transfusion therapy as per nonpregnant women with SCD. Alloantibody screening should occur early in pregnancy and phenotypically matched blood is suggested for transfusion. Folic acid requirements are higher; thus, women should receive 4 to 5 mg daily beginning 2 months preconception and continuing until the end of the first trimester, then the dose may be reduced. Given the increased risk of preeclampsia, low-dose aspirin is recommended from 13 weeks of gestation until 5 to 10 days before delivery.

Thrombocytopenia in pregnancy: what the hematologist needs to know

- Gestational thrombocytopenia is typically associated with a platelet count, between 70,000/μL and 150,000/μL, and most often does not require treatment.
- The evaluation of thrombocytopenia should always include review of the peripheral blood smear, particularly to aid in the distinction between gestational thrombocytopenia, ITP, and microangiopathic hemolytic anemia.
- ITP is commonly detected in the first trimester; corticosteroids such as prednisone and intravenous immunoglobulin (IVIg) are recommended when treatment is required.
- Preeclampsia is diagnosed in the pregnant woman with hypertension and proteinuria or, if proteinuria is absent, evidence of end organ damage. Moderate- and high-risk patients should receive low-dose aspirin.
- HELLP syndrome is characterized by microangiopathic hemolytic anemia, elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and LDH, and thrombocytopenia. Treatment is delivery of the fetus.
- TTP may be congenital or acquired as in the nonpregnant patient. Treatment for acquired TTP is plasma exchange; plasma infusion is indicated in congenital TTP.
- Complement-mediated TMA (complement-mediated hemolytic uremic syndrome [HUS], atypical HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and increased creatinine. Eculizumab is the treatment of choice.
- Acute fatty liver of pregnancy (AFLP) is an obstetric emergency that requires delivery of the fetus and supportive management of the mother.
- Disseminated intravascular coagulation may occur because of pregnancy-related events such as postpartum hemorrhage, amniotic fluid embolism, retained dead fetus, or abruptio placenta. Management is supportive and treatment of the underlying cause. Delivery should not be delayed while awaiting correction of coagulation parameters.
- Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired stem cell disorder characterized by hemolysis, bone marrow failure, and hypoplastic anemia. Treatment is eculizumab and prophylactic or therapeutic-dose low-molecular-weight heparin.

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After anemia, thrombocytopenia is the most common hematologic abnormality of pregnancy. Thrombocytopenia affects approximately 5% to 10% of women during pregnancy or in the immediate postpartum period and results from several disorders that may or may not be specific to pregnancy.

A summary of causes, clinical and laboratory findings, and treatment of thrombocytopenia in pregnancy is presented in Table 3-1. The distribution of the various thrombocytopenic conditions is depicted in Figure 3-1.

Importantly, unless the platelet count is rapidly falling or there is a concurrent bleeding risk such as aspirin or anticoagulant use or inherited platelet dysfunction, pregnant patients with thrombocytopenia can be cleared for an epidural/spinal anesthesia if the platelet count is >70,000/μL, per the recent Society for Obstetric Anesthesia and Perinatology guidelines.

Patients with platelet counts of >50,000/μL but <70,000/μL can be considered for a central neuraxial anesthesia after discussion with the patient, anesthetist and/or anesthesiologist, and conferring hematologist. The platelet count cutoff for delivery should ideally be >50,000/μL. Though there are reports of vaginal delivery below 50,000/μL; in case there is conversion to a cesarean delivery, >50,000/μL is advised. However, in both situations (central neuraxial anesthesia and delivery), it is acknowledged that local practice patterns vary and a discussion with the patient and multidisciplinary team is necessary.

Gestational thrombocytopenia

Gestational thrombocytopenia is defined as a platelet count below 150,000/uL. It accounts for 75% of thrombocytopenia in pregnancy and occurs in 4% to 12% of all pregnancies, usually during the second or third trimester, and rarely in the first trimester in otherwise healthy pregnant women. Thrombocytopenia is usually mild and self-limited, requiring no treatment, and typically does not decrease below 70,000/μL, but on occasion, gestational thrombocytopenia with platelet counts below 50,000/ μL have occurred. The mechanism of gestational thrombocytopenia appears to be multifactorial, including hemodilution and enhanced clearance.

Gestational thrombocytopenia is a diagnosis of exclusion. There are several salient features: (1) onset can be at any point in pregnancy; however, onset is most common in the mid-second to third trimester; (2) the patient is asymptomatic with no prior history of bleeding or thrombocytopenia outside of pregnancy; (3) it has no effect on pregnancy outcome and does not result in thrombocytopenia in the offspring of affected women; (4) it is usually self-limited and resolves 4 to 8 weeks postpartum, but may recur to the same degree in subsequent pregnancies.

Table 3-1 Causes, clinical and laboratory characteristics, and treatment of thrombocytopenia in pregnancy

	ITP	Gestational	Preeclampsia	HELLP	Complement-mediated TMA	TTP	AFLP	DIC	PNH
Neurologic symptoms	−	−	+/−	+	+/−	+/−	+	−	−
Epigastric pain	−	−	+/−	+	+/−	+/−	+	−	−
Vomiting	−	−	+/−	+/−	+/−	+/−	++	−	−
Hypertension	−	−	+	+/−	+/−	+/−	+/−	−	−
Proteinuria	−	−	+/−	+	+	+	+/−	+/−	+
↑LDH	−	−	+	+	++	++	+/−	+/−	+
↓Platelets	++	+	+	++	++	++	+	+	+
↑AST/ALT	−	−	+/−	+	+/−	+/−	++	−	−
↑Creatinine	−	−	+/−	+/−	++	+	+/−	+/−	+/−
↑Uric acid	−	−	+	+	+	+	++	+/−	+/−
↑Bilirubin	−	−	+/−	+/−	+/−	+/−	++	+/−	+
↑PT/PTT	−	−	−	−	−	−	++	+	−
↓Glucose	−	−	−	−	−	−	+/−	−	−
Treatment	Corticosteroids, IVIg	Observation, serial CBCs	Delivery of the fetus	Delivery of the fetus	Plasma exchange, eculizumab, delivery of the fetus	Plasma exchange, delivery of the fetus	Delivery of the fetus, liver transplantation evaluation	Delivery of the fetus	Eculizumab, prophylactic or therapeutic anticoagulation

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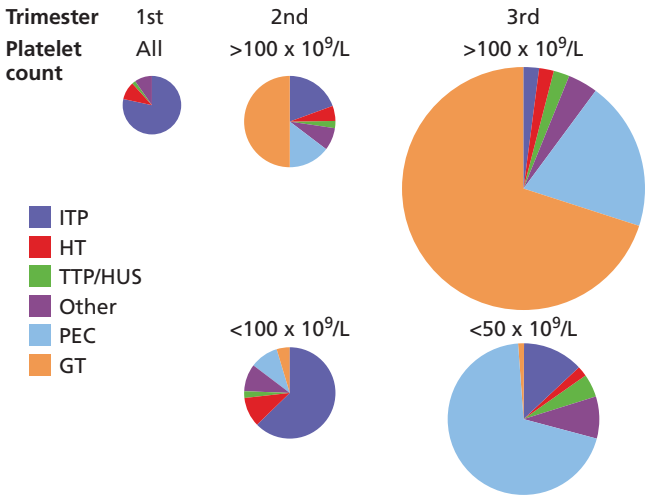

Figure 3-1 Distribution and timing of thrombocytopenic conditions in pregnancy. Prevalence of causes of thrombocytopenia based on trimester of presentation and platelet count. The size of each circle represents the relative frequency of all causes of thrombocytopenia during each of the 3 trimesters of pregnancy. All etiologies and all platelet counts are considered together in the first trimester when thrombocytopenia is uncommon. Distribution of etiologies during the second and third trimesters is subdivided by platelet count. All results are estimates based on personal experience and review of the literature. "Other" indicates miscellaneous disorders, including infection, DIC, type 2B von Willebrand disease, immune and nonimmune drug-induced thrombocytopenia, paroxysmal nocturnal hemoglobinuria, bone marrow failure syndromes (aplastic anemia, myelodysplasia, myeloproliferative disorders, leukemia/lymphoma, and marrow infiltrative disorders), among others. GT, Glanzmann's thrombasthenia; ITP, immune thrombocytopenic purpura; HT, hormone therapy; HUS, hemolytic uremic syndrome; PEC, preeclampsia/hemolysis, elevated liver function tests, and low platelets (HELLP); TTP, thrombotic thrombocytopenic purpura. Redrawn from Cines DB, Levine LD, *Blood*. 2017;130(21):2271-2277, with permission.

Gestational thrombocytopenia may not be distinguishable from ITP or more serious disorders in late pregnancy. However, women with gestational thrombocytopenia should be observed throughout pregnancy, including monitoring the platelet count every 2 to 4 weeks. A fall in the platelet count <70,000/μL in the third trimester would usually be reclassified as ITP or possibly preeclampsia/eclampsia and managed accordingly, because gestational thrombocytopenia can be viewed as being part of a continuum.

Recommendations

No treatment is recommended as the disorder generally resolves postpartum. Recent guidelines suggest the risk of spinal epidural hematoma associated with a platelet count of 70,000/μL or greater is very low in patients with gestational thrombocytopenia.

Immune thrombocytopenic purpura

Immune thrombocytopenic purpura affects approximately 1 in 10,000 pregnancies. In contrast to gestational thrombocytopenia, ITP is usually detected in the first trimester. A prior history of thrombocytopenia or autoimmune disease preceding pregnancy is useful in making a diagnosis of ITP. Patients with ITP generally present with more severe thrombocytopenia than those with gestational thrombocytopenia, but the 2 disorders may be indistinguishable when ITP is mild.

Indications for treatment of ITP in pregnancy in the first 2 trimesters include: (1) when the patient is symptomatic, (2) when platelets fall <30,000/μL, or (3) to increase platelet count to a level considered safe for procedures. Per the recent Society for Obstetric Anesthesia and Perinatology guidelines, a platelet count of 70,000/μL is recommended for neuraxial anesthesia, and most hematologists recommend at least 50,000/μL for cesarean delivery.

Therapy of ITP in pregnancy is similar to that in patients who are not pregnant. Corticosteroids and IVIg are the first-line treatments for maternal ITP. Prednisone is usually given at a dose of 0.5 to 1.0 mg/kg/day, with adjustment to the minimum dose providing a hemostatically effective platelet count. Although short-term prednisone is considered effective and safe in the mother, it may exacerbate hypertension, hyperglycemia, osteoporosis, weight gain, and psychosis; in the fetus, it may increase the incidence of cleft palate if exposure is in the first trimester. Splenectomy is an option in the early second trimester.

Other nonsurgical options can be considered for refractory ITP in pregnancy. IV anti-D has been used successfully to treat ITP in Rh(D)-positive women, although data from only a few patients have been reported, and the safety of this agent cannot be considered established. Similarly, there is little experience with the use of rituximab in pregnant individuals, and B-cell lymphocytopenia has been reported in the offspring of individuals treated with this agent, wherein newborn vaccination would need to be delayed. The thrombopoietic agents romiplostim and eltrombopag may be considered. A recent report suggests temporary off-label use of thrombopoietic agents for severe and/or refractory ITP during pregnancy may be safe for both mother and neonate and results in increased maternal platelet count. The use of cytotoxic therapy is associated with teratogenicity and is generally contraindicated, although azathioprine has been used in pregnancy with apparent safety.

Up to 10% of the offspring of patients with ITP are also thrombocytopenic, and 5% have platelet counts <20,000/μL. There are no maternal laboratory studies that reliably predict whether an infant of a mother

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with ITP will be born thrombocytopenic. Moreover, no maternal interventions have been shown convincingly to increase the fetal platelet count. The delivery of the offspring of mothers with ITP by cesarean delivery has not been shown to reduce the risk of fetal intracranial hemorrhage, a rare complication affecting <1% of these infants at delivery.

Management of ITP antepartum

For pregnant women, prednisone or IVIg is recommended for severe ITP. In those with severe ITP refractory to steroids and IVIg, splenectomy should be considered, optimally in the second trimester. Nonsurgical options for refractory cases would include rituximab, thrombopoietic agents, and cyclosporine, as mentioned in the aplastic anemia and autoimmune hemolytic anemia sections.

Management of ITP peripartum

All offspring of patients with ITP should be monitored closely for the development of ITP within the first 4 to 7 days after delivery, and all thrombocytopenic neonates should undergo cranial ultrasound. For severely affected offspring, IVIg is recommended. Postpartum hemorrhage can be noted in up to a quarter of ITP patients at a median platelet count of ~60,000/μL compared to ~130,000 μL in non-ITP patients. Consequently, consideration of prophylactic tranexamic acid postpartum should be given, particularly if the platelet count is <50,000/μL and certainly if PPH ensues.

Preeclampsia and eclampsia

Thrombocytopenia may also occur in patients with preeclampsia, a hypertensive disorder of pregnancy. Preeclampsia affects 5% to 8% of all pregnancies and develops after 20 weeks of gestation or postpartum; however, it most commonly occurs after 34 weeks of gestation. Currently hypertensive disorders are classified as preeclampsia-eclampsia, chronic hypertension (of any cause), chronic hypertension with superimposed preeclampsia, and gestational hypertension. Eclampsia, defined by the presence of grand mal seizures accompanying preeclampsia, complicates <1% of preeclamptic pregnancies.

Preeclampsia is increasing in prevalence. Significant risk factors for preeclampsia include nulliparity, maternal age 35 and older, prior history of preeclampsia, multifetal gestation, chronic hypertension, diabetes mellitus, systemic lupus erythematosus, renal disease, obesity, assisted reproductive technology (ART), a personal history of preeclampsia, obstructive sleep apnea, sickle cell disease, and the antiphospholipid antibody syndrome.

Diagnostic criteria for preeclampsia include hypertension and proteinuria or, if proteinuria is absent, evidence of end organ damage to include thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or headache. Severe preeclampsia is diagnosed in the subset of women with preeclampsia who have severe hypertension and/or significant end organ dysfunction. Up to 50% of patients with preeclampsia develop thrombocytopenia, the severity of which generally is related to that of the underlying disease. The pathogenesis of thrombocytopenia in preeclampsia is not well understood.

There are limited options for the prevention and treatment of preeclampsia. Observation that endothelial dysfunction occurs in preeclampsia has led to studies of antiplatelet agents, primarily low-dose aspirin, to prevent preeclampsia. Current recommendations include initiation of low-dose (81 mg/day) aspirin for preeclampsia prophylaxis for moderate- and high-risk groups initiated between 12 and 20 weeks of gestation, preferably before 16 weeks of gestation. Magnesium sulfate is used in severe cases of preeclampsia to prevent seizures. The only cure for preeclampsia is delivery. Delivery is indicated at >37 weeks of gestation, or >34 weeks of gestation if there is severe preeclampsia or anytime there is evidence of progressive end organ damage.

Finally, disseminated intravascular coagulation (DIC) also may accompany severe preeclampsia and may be initiated by such processes as retained fetal products, placental abruption, or amniotic fluid embolism. In these settings, DIC can be severe, abrupt, and fatal if not managed appropriately.

Recommendations

Low-dose aspirin (81 mg/day) is recommended to initiate between 12 and 20 weeks of gestation, preferentially prior to 16 weeks of gestation and continuing until delivery, in patients with moderate- to high-risk preeclampsia. Unless severe disease is present, delivery is indicated at 37 weeks of gestation.

HELLP syndrome

HELLP syndrome affects 0.10% to 1% of pregnant women. Some consider HELLP syndrome as one of the more severe forms of preeclampsia given the increased rates of maternal morbidity and mortality. The following diagnostic criteria are used for HELLP: microangiopathic hemolytic anemia, LDH (600 IU/L or more), AST and ALT more than twice the upper limit of normal, and platelet count less than 100,000/μL. HELLP syndrome more commonly occurs in the third trimester; however, 30% of cases either progress to or present postpartum.

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The most common presenting symptoms are right upper quadrant pain and generalized malaise in the majority of cases, 50% of patients present with nausea and vomiting.

In some cases, HELLP may be difficult to distinguish from TTP-HUS. Because many patients with HELLP may present with isolated right upper quadrant and epigastric pain in the absence of hypertension and proteinuria, patients may be misdiagnosed as having primary gastrointestinal disease and even referred for surgical consideration. HELLP is associated with significant maternal and fetal morbidity and mortality; therefore, prompt diagnosis and treatment are essential.

In HELLP syndrome, red cells, platelets, fresh frozen plasma (FFP), or cryoprecipitate (for hypofibrinogenemia) may be necessary during and after delivery. Laboratory values may worsen in the first 48 hours after delivery; thus, careful postpartum monitoring is essential. If persistent, severe postpartum HELLP occurs, consideration may be given to treatment with steroids and plasmapheresis. The offspring of patients with both preeclampsia and HELLP also may become thrombocytopenic, although the thrombocytopenia is usually mild.

Therapy for HELLP and preeclampsia is directed toward stabilization of the mother, followed by expeditious delivery, after which, for the majority of patients, these disorders usually remit within 3 to 4 days. One should consider the use of adjunctive therapies as noted previously if thrombocytopenia continues to worsen or there is continuing clinical deterioration 5 to 7 days after delivery.

Recommendations

Expeditious delivery of the fetus and supportive care of the mother is recommended, including transfusion support through delivery. Close monitoring of the mother following delivery is recommended. Consideration may be given to corticosteroids and plasma exchange if platelet or coagulation abnormalities persist postpartum in a patient with severe HELLP.

Thrombotic thrombocytopenic purpura

It is estimated that acquired TTP occurs in 1 in 200,000 pregnancies, whereas 25% to 50% of women with congenital TTP present for the first time during pregnancy or postpartum. TTP may occur at any time during pregnancy; however, presentation is most common in the third trimester and postpartum period. The rate of fetal loss is increased, particularly in untreated congenital TTP and acquired TTP that occurs in the first or second trimester. An ADAMTS13 activity of less than 10% confirms the diagnosis of TTP. Plasma exchange is the mainstay of therapy for acquired TTP, similar to nonpregnant patients. If there is a delay in initiating plasma exchange, then plasma infusion is recommended. Plasma infusion is also recommended for patients with congenital TTP (Upshaw-Schulman syndrome). At this time there is no information regarding the safety of caplacizumab (anti–von Willebrand factor humanized immunoglobulin) during pregnancy.

Recommendations for acquired TTP

Plasmapheresis is the preferred therapy, similar to nonpregnant patients. Concurrent use of corticosteroids can be considered however there is a lack of robust data. There is little published guidance on the use of rituximab in pregnancy and the safety of caplacizumab is unknown. The risk of recurrence in a subsequent pregnancy is greater than 50% for those women with persistent severely reduced ADAMTS13 activity. Plasmapheresis can be considered in this scenario when plasma levels of ADAMTS13 decrease to less than 5% to 10%.

Recommendations for congenital TTP

Prophylactic plasma infusions of at least 10mL/kg every 2 weeks are recommended at confirmation of pregnancy. During the second or early third trimester, the frequency of plasma infusions is increased to weekly. Plasma therapy and close monitoring for relapse are continued until 6 weeks postpartum.

Complement-mediated TMA

The incidence of complement-mediated TMA or complement-mediated HUS, also referred to as atypical HUS, is increased in association with pregnancy. Up to 80% of women who develop complement-mediated TMA develop manifestations in the postpartum period. Differentiation from TTP may be difficult until renal failure becomes the predominant feature. Diagnostic features include microangiopathic hemolytic anemia, thrombocytopenia, and increasing serum creatinine. The prognosis of postpartum complement-mediated TMA is poor, with persistent renal failure in >25% of affected individuals. Although responses to plasma exchange have been reported, the overall response rate to this intervention is low; nevertheless, a trial of plasma exchange is indicated, particularly given the difficulty in distinguishing TTP and complement-mediated TMA. Institution of anticomplement therapy with eculizumab is recommended when complement-mediated TMA is considered the most likely diagnosis, as end-stage renal disease may rapidly occur.

Recommendations

Treatment in terms of plasma exchange is similar to that for acquired TTP but if the ADAMTS13 level returns

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normal, eculizumab should be initiated for complement-mediated TMA. All patients receiving eculizumab require meningococcal vaccination and antibiotic prophylaxis against encapsulated organisms. Dialysis may be required for those who develop end-stage renal disease.

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy is considered an obstetric emergency. It is associated with maternal liver dysfunction and/or failure that can result in maternal and fetal complications. The pathogenesis is unclear; however, defects in fatty acid metabolism have been suggested as a causative mechanism. Patients typically present in the third trimester, although AFLP may rarely occur as early as the first trimester or as late as following delivery. Symptoms include nausea, vomiting, right upper quadrant pain, anorexia, jaundice, and cholestatic liver dysfunction. Hypoglycemia is present in >50% of cases. Thrombocytopenia is usually mild, but maternal bleeding is common because of the accompanying coagulopathy resulting from diminished hepatic synthesis of coagulation proteins. Acquired antithrombin deficiency may also occur, and in rare cases could lead to thrombosis. The Swansea criteria is a diagnostic model for AFLP that has been validated in a cohort study. The Swansea criteria include vomiting, abdominal pain, polydipsia/polyuria, encephalopathy, elevated bilirubin, hypoglycemia, leukocytosis, elevated transaminases, elevated ammonia, elevated urate, acute kidney injury or elevated creatinine, coagulopathy, ascites, and microvesicular steatosis on liver biopsy. The presence of 6 or more abnormal variables has been shown to have a positive predictive value of 85% and negative predictive value of 100% for microvesicular steatosis. Management includes prompt delivery of the fetus regardless of gestational age.

Recommendations

For AFLP, delivery of the fetus and supportive management of the mother, and coagulation support for liver dysfunction or DIC, if present, is recommended. Although liver function may recover, patients should undergo liver transplant evaluation.

Disseminated intravascular coagulation

DIC is a disruption of the balance of hemostasis characterized by systemic activation of coagulation that results in generation and deposition of fibrin and formation of microvascular thrombi in the microvasculature. Concurrently, activation of plasmin results in fibrinolysis and hemorrhage. Because of widespread thrombi formation, platelets and clotting factors are consumed, resulting in further bleeding. The primary inciting factor in DIC is excess exposure to tissue factor; thus, DIC may occur secondary to postpartum hemorrhage, retained dead fetus, amniotic fluid embolism, or placental abruption. It may also complicate severe preeclampsia/HELLP, AFLP, or puerperal sepsis. If DIC develops or persists following delivery, evaluation for retention of fetal products is recommended. Management of DIC is supportive; delivery should not be delayed while awaiting correction of coagulation parameters. Supportive measures may include administration of platelets, FFP, and cryoprecipitate, and early replacement of fibrinogen with cryoprecipitate and/or fibrinogen concentrates should severe bleeding occur.

Recommendations

Underlying conditions that are causative for DIC should be treated accordingly. Delivery of the fetus and supportive management of the mother is recommended; platelets, FFP, and cryoprecipitate may be given to replace platelets and coagulation factors that are consumed. Frequent monitoring of fibrinogen and early replacement of fibrinogen with cryoprecipitate and/or fibrinogen concentrates are recommended.

Paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria is a rare, acquired stem cell disorder characterized by hypoplastic anemia, bone marrow failure, and hemolysis caused by increased susceptibility of red cells to complement-mediated lysis. The defect is a mutated phosphatidyl inositol gene (*PIG-A*), the anchor of the complement regulatory CD55 and CD59 proteins, to the red blood cell membrane. This defect results in loss of regulation of the terminal complex C5β-9, leading to red blood cell lysis. In addition to hemolysis, PNH is characterized by arterial and venous thrombosis; thrombotic risk correlates with expression of GPI-linked proteins on the surface of granulocytes, with the greatest risk associated with a PNH clone >50%.

Maternal and fetal morbidity and mortality are higher among pregnant women with PNH primarily because of thromboembolism in the mother and premature birth. Because of the high risk of VTE in pregnant women with PNH, antithrombotic therapy is recommended postpartum, and antepartum prophylaxis is indicated for patients with large PNH clones (>50%), prior history of VTE, or recurrent prior late fetal loss. Eculizumab is a humanized monoclonal antibody against complement protein C5 that inhibits terminal complement activation. Studies in pregnancy suggest that the benefits outweigh the potential risks, with increased fetal survival and a low rate of maternal complications.

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Recommendations

For pregnant women with PNH, prophylactic or therapeutic-dose low-molecular-weight heparin (LMWH) is recommended based upon increased thromboembolic risk or history of thromboembolism and should be continued for 6 to 12 weeks postpartum. Use of eculizumab during pregnancy appears to carry greater benefit than risk and is recommended in pregnant women with PNH.

Hematologic health issues in pregnant women: bleeding and clotting disorders

Bleeding disorders in pregnancy: what the hematologist needs to know

- A multidisciplinary approach to preconception and delivery management is needed.
- The levels of von Willebrand factor (VWF) increase throughout pregnancy. Repeat VWF antigen and activity levels at 34 to 36 weeks' gestation can help guide neuraxial anesthesia and delivery management for patients with von Willebrand disease (VWD).
- There is a risk of secondary (delayed) postpartum hemorrhage for patients with VWD and other bleeding disorders. Use of postpartum antifibrinolytics can decrease bleeding.
- In women with hemophilia in whom an affected infant is anticipated, instrumentation should be avoided, and cesarean delivery should be offered.

Postpartum hemorrhage in women with bleeding disorders

Postpartum hemorrhage is a major cause of morbidity and mortality in childbirth; women with an underlying bleeding disorder are at greater risk for PPH. While several single-center studies have reported PPH in up to a third of cases (most with VWD), population-based studies indicate lower rates of PPH, about 1.5-fold greater than women without a bleeding disorder. A summary of the management of bleeding disorders in pregnancy, including preferred agents, target levels, and dosing, is found in Table 3-2. The most common causes of PPH in the general obstetric population are uterine atony, retained placenta/products of conception, and genital tract trauma.

Table 3-2 Specific factor replacement in inherited bleeding disorders peripartum

Factor deficiency	Patients' factor level (normal)	Desired level	Recommendation
VWD type 1	<50%	>100%	VWF concentrate 40-60 IU/kg, then 20-40 IU/kg q 12 h, then daily 3-5 days if vaginal delivery, 5-7 days if cesarean
VWD types 2, 3	<50%	>100%	VWF concentrate 60-80 IU/kg, then 40-60 IU/kg q 12 h, then daily 3-5 days if vaginal delivery, 5-7 days if cesarean
FI (fibrinogen)	<0.5 g/L	1-1.5 g/L × 3 days	Pregnancy prophylaxis: fibrinogen concentrate 50-100 mg/kg twice a week to maintain level at >1 g/L (more during labor) × 3 days. Cryoprecipitate 15-20 mL/kg, SD-FFP 15-30 mL/kg. TXA 15-20 mg/kg IV, then 1 g po TID
FII	<20% (50%-150%)	20%-40%	PCC 20-40 U/kg, then PCC 10-20 IU/kg q 48 h to maintain levels for at least 3 days
FV	<20% (50%-150%)	20%-40%	FFP 15-20 mL/kg, later FFP 10 mL/kg q 12 h for at least 3 days. For severe bleeding or cesarean, give platelet transfusion (FV+VIII give DDAVP, FFP)
FVII	<20% (50%-150%)	>40%	rFVlla 15-30 μg/kg q 4-6 h for at least 3-5 days
FVIII, FIX	<50% (50%-150%)	>100%	FVIII carrier: FVIII concentrate 20-40 IU/kg; FIX carrier: 40-50 IU/kg
FX	<30% (50%-150%)	>40%	PDFX concentrate 1500 U (18.8-25 U/kg), PCC 10-20 U/kg qd × 3 days, FFP
FXI	<15%-20% (70%-150%)	>30%-40%	If bleeding phenotype or prior h/o PPH-FXI concentrate 15-20 U/kg if available; FFP, TXA alone at 1 g qtg. rFVlla for FXI inhibitors
FXIII	<30% (70%-150%)	>20%	PdFXIII 20-40U/kg × 1, rFXIII-A 35U/kg, cryoprecipitate, FFP

Adapted from Pavord S et al, *BJOG* 2017;124:e193-e263, with permission. It should be recognized that these represent expert opinion recommendations, and treatment duration and intensity are based on not only the factor level but historical assessment of the bleeding phenotype.

DDAVP, 1-desamino-8D-arginine vasopressin; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; PDFX, plasma-derived FX; PdFXIII, plasma-derived FXIIII; PPH-FXI, postpartum hemorrhage-FXI concentrate; rFVlla, recombinant activated factor VII; rFXIII-A, recombinant FXIII; SD-FFP, solvent detergent fresh frozen plasma; TXA, tranexamic acid; VWD, von Willebrand disease; VWF, von Willebrand factor.

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Women with inherited bleeding disorders can have these same risk factors, as well as the additional risk factor of their coagulation defect. In the general population, most PPHs are primary (within 24 hours of delivery). In women with bleeding disorders, secondary PPH (24 hours to 6 weeks postpartum) is much more common and has been reported in up to 25% of women with inherited bleeding disorders. Risk factors for uterine atony include prolonged induced or augmented labor and expectant rather than active management of the third stage of labor. Therefore, in women with inherited bleeding disorders, these factors should be minimized to reduce the risk of PPH. Hemostatic management also may reduce the risk of PPH. Factor levels should be assessed in the third trimester of pregnancy, and prophylactic factor replacement given at delivery to those with subtherapeutic levels (Table 3-2). Finally, care must be taken to minimize genital and perineal trauma to reduce the risks of both PPH and perineal hematomas. Perineal (or vulvar) hematomas, a rare complication of vaginal birth, occur with some frequency in women with bleeding disorders and contribute to the increased incidence of PPH. In one patient series, the prevalence of perineal hematoma was much higher in women with inherited bleeding disorders (1% to 6%) as compared to a reported 0.2% in the general population. Even after discharge from the hospital, women with inherited bleeding disorders require close follow-up during the postpartum period. In the general obstetric population, the median duration of bleeding after delivery is 21 to 27 days. A case-control study revealed that women with inherited bleeding disorders have significantly longer postpartum bleeding duration than controls, even when they receive appropriate hemostatic treatment. In VWD, the pregnancy-induced increase in coagulation factor levels starts to decline 3 to 7 days after delivery and return to prepregnancy levels within 14 to 21 days of delivery. Therefore, close postpartum monitoring of women with bleeding disorders is recommended for, at minimum, 3 weeks and up to 6 weeks. Figure 3-2 depicts the continuum of obstetrical and hematological interventions in the prevention and treatment of PPH.

von Willebrand disease

VWD is the most common inherited bleeding disorder. Although approximately 1% of the general population is affected, only 0.1% are symptomatic, and many are unaware of their diagnosis. Please see Chapter 10 to review the clinical features, laboratory diagnosis, and management of VWD outside of pregnancy.

Presumably under the regulation of estrogen that occurs in pregnancy, the levels of VWF and factor FVIII increase, although not as high as the increase seen physiologically in a normal pregnancy, which may explain the increased risk of PPH in VWD and evolving consensus to replace to a level >~100% as opposed to historically ~50%. In general, the rise begins in the early second trimester and peaks between 29 and 35 weeks. For this reason, a diagnosis of VWD may be masked if VWF levels are performed when a patient is pregnant, particularly within 6 to 8 weeks of delivery. Thus, whenever possible, the preconception VWF level and bleeding history should be established. During pregnancy, most patients with type 1 VWD normalize their levels of VWF and FVIII, although those with more severe disease may not. Given the somewhat unpredictable nature of these responses, measurement of VWF levels should be performed around 34 to 36 weeks; levels generally remain fairly stable through the remainder of pregnancy, and thus levels obtained at this time allow for a delivery plan to be developed. Although levels of VWF may increase in patients with type 2 VWD, functional levels may not be significantly enhanced because of the production of a functionally defective protein. Levels of VWF generally do not increase during pregnancy in patients with type 3 VWD.

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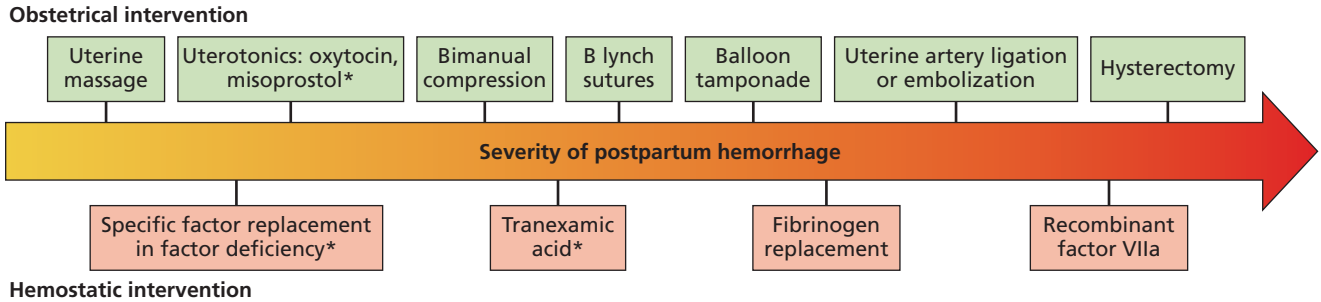
Figure 3-2 The continuum of obstetrical and hemostatic interventions in the prevention and treatment of PPH. The asterisk denotes consideration in prevention of PPH if underlying bleeding disorder and/or placental previa, twin gestation, or antepartum hemorrhage. Redrawn from Kouides PA, *Blood Adv.* 2017;1(11):699-702, with permission.



In most cases, the physiologic increase in VWF during pregnancy exceeds the minimum 50-IU/dL VWF level recommended for epidural anesthesia in type 1 VWD. Based on case reports and expert opinion, it is recommended that pregnant women with type 1 VWD and VWF levels <50 IU/dL in the eighth month of pregnancy, and those with type 2 or 3 VWD, receive VWF concentrate at the time of active labor up to 3 to 7 days postpartum. Central neuraxial anesthesia is safe in type 1 VWD after achieving a VWF level >50%. But regarding types 2 and 3 VWD, the 2017 Royal College of Obstetricians and Gynaecologists guidelines advise "that neuraxial anesthesia be avoided unless VWF activity is more than 50% and the haemostatic defect has been corrected; this may be difficult to achieve in type 2 and central neuraxial anesthesia should not be given in cases of type 3." In type 2N, central neuraxial anesthesia is safe if the FVIII level is replaced to >50%. Thereafter, it is generally judicious to remove the catheter as soon as possible after delivery is completed.

Several therapeutic options are available around labor and delivery. VWF concentrate is recommended for patients with type 1, 2, or 3 VWD and is continued for up to 3 to 7 days postpartum, as required by disease severity and mode of delivery (Table 3-2). Desmopressin (1-desamino-8D-arginine vasopressin [DDAVP]) is an alternative option for patients with type 1 VWF if the patient has been documented to be a responder in the past, but it must be used very cautiously because of the risk of hyponatremia in the setting of often vigorous fluid replacement with hypotonic fluids. Women commonly receive 1 to 2 L of fluid at the time of vaginal delivery and 2 to 3 L at the time of cesarean delivery, and DDAVP may result in fluid retention, life-threatening hyponatremia, and/or seizures. However, in an excellent DDAVP responder and in a very controlled setting where fluids and electrolytes can be carefully monitored, both the 2017 United Kingdom and National Hemophilia Foundation guidelines allow for DDAVP use—albeit with caution.

Regarding replacement therapy, the historic target level was 50% or higher, but recent studies strongly suggest undertreatment resulting in increased blood loss. Therefore, postpartum replacement ideally should aim for VWF levels >~100 IU/dL (ie, closer to levels that are observed in unaffected pregnant women). It is possible that the undertreatment is in part also because the dosing is not weight-based, that is, taking into consideration the increased plasma volume peripartum.

Postpartum, the decline in VWF levels generally occurs over 2 to 3 weeks, and may be unpredictable and occasionally precipitous; thus, the period of 3 to 6 weeks postpartum is considered a particularly vulnerable time for postpartum bleeding and close follow-up is recommended. Not only is postpartum bleeding more common in pregnant women with VWD, so too is transfusion requirement, longer hospital length of stay, and mortality, which may be up to 1.2%.

Regarding adjunctive use of antifibrinolytic therapy, in considering the risk/benefit, it would seem reasonable to use tranexamic acid, 1 g IV load at delivery in the type 2 or 3 VWD patient and the "severe" type 1 patient who has not normalized their levels in the third trimester. Tranexamic acid can be considered thereafter in these patients at 1 to 1.3 g orally 3 times a day for 7 to 21 days postpartum. In type 1 patients who have normalized their VWF levels, expectant management without prophylactic antifibrinolytic therapy is reasonable postpartum unless they have undergone a cesarean delivery or have a prior history of PPH or are otherwise at an increased of bleeding. Monitoring for bleeding is recommended for at least 3 weeks, as noted previously.

Recommendations

VWF antigen and activity levels should be repeated at 34 to 36 weeks of gestation, and if >50% for type 1 VWD, then they can receive neuraxial anesthesia. VWF concentrate is recommended for patients with type 1, 2, or 3 VWD based on disease severity and is continued for up to 3 to 7 days postpartum. While DDAVP remains an alternative, cautious use, including electrolyte monitoring is needed given the serious risk of hyponatremia with excess fluids around delivery. Given the dropping VWF levels postpartum and delayed PPH risk, the use of regular tranexamic acid for 7 to 21 days postpartum helps to minimize serious bleeding.

Hemophilia carriers

Postpartum bleeding may occur in 10% of hemophilia carriers and may lead to significant blood loss and anemia, in some cases requiring transfusion. Interestingly, the factor level does not predict bleeding risk: up to 30% of hemophilia carriers, even with normal factor VIII and IX levels, may have high bleeding scores; and up to 30% may be considered to be mild hemophilia with contributing factors for low levels including the type of mutation, the degree of skewed X chromosome (extreme lyonization) and concurrent VWF level, which in turn can be influenced by the ABO type.

In the hemophilia carrier expecting an affected infant, the risk of intracranial hemorrhage is 2.5% compared to 0.06% in the general population (odds ratio 44-fold) and the risk of extracranial hemorrhage is 3.7% compared with 0.47% (odds ratio 8-fold). The majority of cases of

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cranial bleeding were caused by instrumentation (vacuum extraction or forceps). Nonetheless, although not proven conclusively because of a lack of randomized data, cesarean delivery is recommended over vaginal delivery to reduce that risk. In high-risk infants, the critical issue is the availability of a multidisciplinary team in an obstetric unit with facilities for high-risk deliveries. Preconception counseling with genotyping is currently available, as well as pre- and postimplantation options, including preimplantation genetic diagnosis and postimplantation fetal DNA sex determination, chorionic villus sampling, and amniocentesis.

Recommendations

For hemophilia A (or B) carriers with FVIII (or factor IX [FIX]) levels <50 IU/dL or severe past bleeding history, recombinant FVIII (or FIX) concentrate is recommended at the time of neuraxial anesthesia and continued for up to 3 to 7 days postpartum, ideally aiming for a target factor level of >100 IU/dL). In women with hemophilia in whom an affected infant is anticipated, because of the potential risk of central nervous system bleeding, cesarean delivery should be offered. Vacuum extraction and forceps should be avoided because of the risk of cephalohematoma and intracranial hemorrhage. A team approach, including the obstetrician, anesthesiologist, and hematologist, and communication regarding delivery planning and factor replacement, is critical in managing carriers. FVIII concentrate is preferred over the use of desmopressin for delivery. Although mild hemophilia A carriers may prefer desmopressin for treatment of minor procedures akin to its use in VWD patients, as noted previously, it is discouraged at delivery because of the risk of hyponatremia.

Rare bleeding disorders

Rare bleeding disorders include inherited deficiencies of coagulation factors I, II, V, VII, X, XI, and XIII, which represent 5% of all inherited bleeding disorders. There is a wide spectrum of bleeding severity, from none to severe, and it is difficult to predict bleeding risk. Thus, a diagnosis of a rare bleeding disorder may not come to clinical attention until a woman, even with prior bleeding history, experiences postpartum bleeding. In general, risk is related to factor levels, but not entirely. The key to optimal delivery management is awareness of the diagnosis, testing the appropriate factor level at the eighth month of pregnancy, and replacement therapy at delivery for factor deficiency. Because coagulation factors generally increase during pregnancy, a diagnosis may be masked and testing should precede pregnancy whenever possible. In particular, factors I, VII, VIII, VWF, X, XII, and XIII increase during pregnancy, whereas factors II, V, IX, and XI show minimal or no increase. In general, fibrinogen levels of >1.0 to 1.5 g/L, FII >20 to 40 IU/dL, FV >20 to 40 IU/dL, FVII >40 IU/dL, FX >40 IU/dL, FXI >30 to 40 IU/dL, and FXIII >20 IU/dL are recommended, respectively, for each deficiency state, at the time of delivery (Table 3-2). Severe bleeding disorders are likely to be autosomal recessive. For an affected woman (or asymptomatic heterozygous carrier), her risk of having an affected infant should be assessed. When possible, preconception counseling should be provided and genetics and reproductive choices should be discussed. The possibility of consanguinity should be established. Although prenatal diagnosis with chorionic villus sampling and amniocentesis is possible, few obtain it, given the associated 1% to 2% fetal loss. For an affected woman (or asymptomatic heterozygous carrier) with the potential for an affected infant, cesarean delivery should be offered to reduce the risk of intracerebral hemorrhage. As noted, a team approach with a coordinated management plan optimizes outcomes for affected women.

Recommendations

For an affected woman or a known asymptomatic heterozygous carrier, consanguinity should be established, and if so, cesarean delivery should be offered to reduce the risk of intracerebral hemorrhage. In general, central neuraxial anesthesia should be avoided unless replacement can adequately restore hemostasis fully. Based on expert opinion, for rare bleeding factor deficiency states, FFP or factor concentrate to bring factors to hemostatic levels (Table 3-2) is recommended at the time of active labor and for 3 to 4 days postpartum after vaginal delivery and up to 5 to 7 days after cesarean delivery. Adjunctive treatment with TXA be considered at delivery and postpartum based on that patient's historical bleeding phenotype.

Hypofibrinogenemia

Fibrinogen abnormalities, including afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia may be associated with hemorrhagic and thrombotic pregnancy complications, including PPH, spontaneous abortion, and placental abruption. Up to 30% of patients with congenital fibrinogen deficiency have thrombotic complications, most commonly first-trimester abortion; this is common in those with afibrinogenemia, but less frequent in those with hypofibrinogenemia or dysfibrinogenemia. Fibrinogen plays an important role in placental implantation and maintenance of placental competency during pregnancy. When defects in fibrinogen conversion to fibrin occur during pregnancy—whether from deficient or defective fibrinogen—placental separation, miscarriage,

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spontaneous abortion, and hemorrhage may occur. The high rate of pregnancy complications may be reduced by fibrinogen replacement (Table 3-2). Several experts suggest that fibrinogen replacement should be initiated as early as possible in pregnancy.

Recommendations

For pregnant women with fibrinogen <0.5 g/L, prophylaxis throughout pregnancy with fibrinogen concentrate, initially 50 to 100 mg/kg twice weekly adjusted to maintain fibrinogen activity >1 g/L to achieve a level of 1.5 g/L during labor and for 3 days postpartum. For pregnant women with thrombotic dysfibrinogenemia, afibrinogenemia, or hypofibrinogenemia and other risk factors for VTE, thromboprophylaxis should be considered.

Factor XIII deficiency

Factor XIII deficiency is a rare disorder, occurring in 1 in 2 million people, and is associated with pregnancy loss in more than 90% of cases. Long-term prophylaxis is advised in all factor XIII–deficient patients with a personal or family history of bleeding and those with FXIII activity <0.1 IU/mL.

Recommendations

For pregnant women with factor XIII deficiency, it is recommended that the frequency of prophylaxis be increased from every 4 weeks to 10 to 40 IU/kg every 2 to 3 weeks, aiming for a FXIII activity above 20 IU/dL. At the time of delivery, an additional dose of 10 to 40 IU/kg is advised.

Thromboembolism and thrombophilia in pregnancy: what the hematologist needs to know

- The risk of VTE is increased during pregnancy and postpartum, and the most common presentation in pregnancy is a left leg deep vein thrombosis.
- Direct oral anticoagulants should not be used in pregnancy or while breastfeeding.
- Once or twice daily LMWH is recommended for the treatment of VTE in pregnancy, and therapeutic LMWH should be continued for a minimum of 3 months and include the 6 weeks postpartum period.

Pregnant women are at increased risk of developing VTE, which includes deep vein thrombosis and pulmonary embolism. Pulmonary embolism (PE) remains a leading cause of maternal mortality. There is a 5- to 10-fold increased risk of VTE, and VTE affects approximately 1.2 per 1000 pregnancies (0.82-1.99 of 1000 pregnancies), compared to age-matched nonpregnant women (~1 in 10,000 nonpregnant women). Reports vary on the incidence of antepartum versus postpartum VTE events, but in a systematic review there was roughly the same VTE incidence in the antepartum and postpartum periods. During the shorter 6-week postpartum period, the per-day risk of VTE is highest at approximately 15- to 35-fold, compared to age-matched nonpregnant controls. Postpartum, the VTE risk is highest in the first 6 weeks and gradually returns to normal at 12 weeks postpartum. Deep vein thrombosis (DVT) is more common than PE in pregnancy, and most commonly affects the left leg. The majority of pregnancy-associated PE occurs in the postpartum period.

There are adaptive changes in pregnancy of hypercoagulability, as well as venous stasis, and vascular damage that contribute to the increased VTE risk seen. Hypercoagulable changes of the blood and hormone-induced vasodilation are present starting in early first trimester. There is an increase in procoagulant factors (increased factor V, VIII, X, fibrinogen, von Willebrand factor) and a decrease in anticoagulant proteins (decreased protein S level, activated protein C resistance). There is less thrombus breakdown because of decreased levels of tissue plasminogen activator (tPA), increased plasminogen activator inhibitor 1 (PAI-1) and increased placenta-derived PAI-2. D-dimer levels, a marker of fibrinolysis, increase as pregnancy advances. The vessel changes in pregnancy include progesterone-induced vasodilation, the right iliac artery causing compression of the left iliac vein, and pelvic compression from a gravid uterus. Given these anatomical changes, because of the anatomic compression of the left iliac vein, the most common presentation is a left leg DVT in the iliofemoral veins. Vascular damage can occur because of endothelial distension and during vaginal or cesarean delivery.

Additional risk factors increase VTE risk during pregnancy and the postpartum period and include inherited thrombophilia and situational risk factors. Inherited thrombophilia accounts for approximately half of VTE events in pregnancy and the postpartum period. The risk of VTE varies based on the type of thrombophilia and if a family history of VTE is present. Some examples of situational risk factors include prepregnancy body mass index (BMI), varicose veins, chronic inflammatory conditions, bedrest during pregnancy, preeclampsia, unplanned cesarean delivery, postpartum hemorrhage, and infection (Figure 3-3). While the majority of single situational risk factors only modestly increase the risk of VTE, certain combinations of risk factors are more than additive so can increase the VTE risk considerably (eg, prepregnancy BMI and bedrest during pregnancy).

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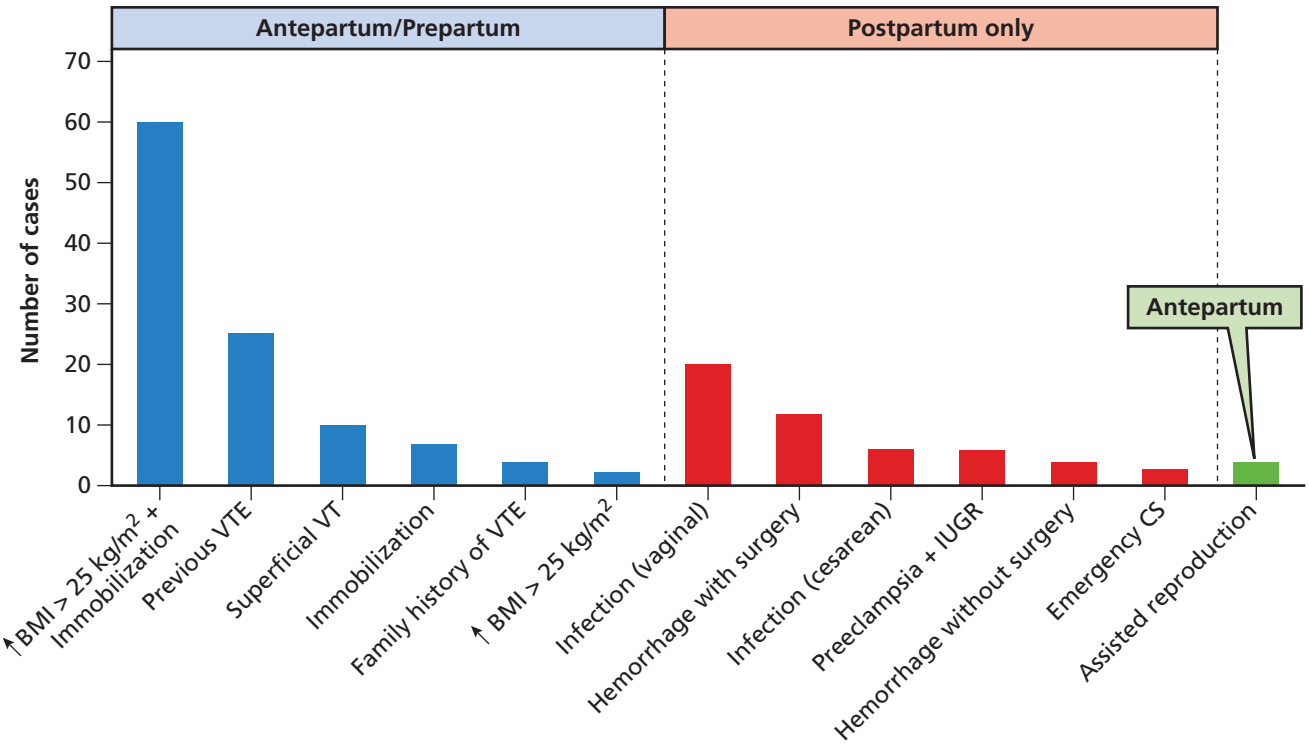

Figure 3-3 Odds ratios of prepartum, antepartum, and postpartum risks (notwithstanding specific genetic thrombophilia). BMI, body mass index; CS, cesarean section; IUGR, intrauterine growth restriction; VT, vein thrombosis; VTE, venous thromboembolism. Data from Bourjeily G et al, *Lancet*. 2010;375(9713):500-512 (© 2010 Elsevier Ltd).

Diagnosis of VTE in pregnancy

If a DVT is suspected in pregnancy, an ultrasound should be ordered as the first diagnostic test. A D-dimer level will often be elevated in pregnancy, especially in the second and third trimesters. In the absence of a validated clinical prediction rule for suspected DVT in the pregnant population, a D-dimer level should not be used. If a single proximal leg ultrasound is negative, then serial leg doppler ultrasounds are recommended to rule out a DVT. If there is a high suspicion for an isolated pelvic vein DVT (eg, whole-leg swelling, or groin, buttock, flank, or abdominal pain) then magnetic resonance imaging (MRI) should be urgently completed.

There have been recent advances in the diagnosis of suspected PE in pregnancy with recent prospective cohort studies that have successfully used a clinical prediction rule of the YEARS (a simplified diagnostic scheme for pulmonary embolism) criteria or the revised Geneva score, in combination with doppler ultrasound imaging of the leg and a D-dimer level. A ventilation perfusion (V/Q) scan or a computed tomographic pulmonary angiography (CTA) are both safe and well below the risk threshold of fetal radiation of 50 mGy, with V/Q scans preferred when available because of less radiation exposure to proliferating maternal breast tissue.

Recommendations

If DVT is suspected, then a leg ultrasound is recommended as the first diagnostic test. If the leg ultrasound is negative, then serial ultrasounds are recommended, or a pelvic MRI should be completed if there is a high suspicion for an isolated iliofemoral DVT. If PE is suspected, both ventilation–perfusion scans or CTA are safe.

Anticoagulant use in pregnancy and postpartum

The anticoagulant of choice in pregnancy is LMWH (Table 3-3). LMWH (as well as unfractionated heparin [UFH]) does not cross the placenta, and numerous studies have confirmed its use is safe for the fetus. Compared to UFH, LMWH is associated with less bleeding risk, a more predictable anticoagulant response, lower risk of heparin-induced thrombocytopenia (HIT) and less bone density loss. Adverse effects of LMWH include antepartum bleeding (~0.5%-1.5%), postpartum bleeding (~1%-2%), adverse skin reactions (~2%-30%), wound hematomas and, rarely, HIT. Therapeutic and prophylactic-dose UFH decrease bone mineral density and a 2% incidence of vertebral fractures have been reported when administered throughout pregnancy. No bone mineral density loss was seen in prospective studies evaluating prophylactic or intermediate doses of LMWH.

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Table 3-3 Features of anticoagulants used or contraindicated in pregnancy

Agent	Pros	Cons
Danaparoid	Can be used in HIT Does not appear to cross the placenta	Injection Not available in the United States
Direct oral anticoagulants	Can consider postpartum in nonbreastfeeding patients, unknown information relating to excess vaginal bleeding in this setting	Cannot be used in pregnancy as they cross the placenta Cannot be used if breastfeeding
Fondaparinux	Can be used in HIT Once-daily dosing	Injection Does cross the placenta Probably safe in breastfeeding
Low-molecular-weight heparin (LMWH)	Does not cross the placenta Most bioavailable of agents, allowing daily to BID dosing Lower rate of HIT than UFH Can be used if breastfeeding	Injection Costlier than UFH
Unfractionated heparin (UFH)	Does not cross the placenta Can be used if breastfeeding	Injection Moderate risk of osteoporosis with use through pregnancy Risk of HIT
Vitamin K antagonists (warfarin)	Can use postpartum including if breastfeeding	Does cross the placenta with 4%–10% risk of embryopathy, increased fetal loss, and neurodevelopmental abnormalities

HIT, heparin-induced thrombocytopenia.

Vitamin K antagonists (VKA) are embryopathic and fetotoxic. Warfarin is teratogenic, causing an embryopathy consisting of nasal hypoplasia, stippled epiphyses, and limb hypoplasia. The frequency of these abnormalities is estimated to be between 4% and 10%. The teratogenic effects occur primarily following exposure to warfarin during weeks 6 to 12 (primarily 6 to 9 weeks) of gestation, whereas warfarin is probably safe preconception and during the first 6 weeks of gestation. VKAs used during pregnancy have not only been associated with birth defects, but also with fetal loss, fetal hemorrhage, and rare central nervous system developmental abnormalities such as dorsal midline dysplasia and ventral midline dysplasia, leading to optic atrophy. Finally, an increased risk of minor neurodevelopmental abnormalities may occur in the offspring of women exposed to warfarin during the second and third trimesters, although the significance of these problems is uncertain. Warfarin may cause a dose-dependent anticoagulant effect in the fetus and may lead to bleeding at delivery. In very select cases, warfarin may be used during the pregnancy for patients with mechanical heart valves when the risk of maternal thromboembolism outweighs these risks.

The direct oral anticoagulants (DOACs), including anti-Xa inhibitors (rivaroxaban, apixaban, edoxaban, betrixaban) and direct thrombin inhibitors (dabigatran), should not be used in pregnancy. Animal studies show increased reproductive risk with implantation loss, congenital malformations, altered ossification, and hemorrhage. To date, no specific signal for congenital defects have been identified in pregnant patients who have been exposed to DOACs, but the data is still limited. If there is an inadvertent DOAC exposure in pregnancy, pregnancy termination is generally not recommended and the patient should be switched to LMWH.

Patients who are already on oral anticoagulation for prior VTE should be counseled on anticoagulant options preconception. Options include continuing on the oral anticoagulant preconception until pregnant with close vigilance and pregnancy test monitoring (and then switching to LMWH once pregnant). If the patient is on a VKA and switches to LMWH, oral vitamin K can be given in an attempt to reverse warfarin. The alternative option is switching to LMWH preconception (with downsides of increased cost and a longer duration on daily injections).

Postpartum, LMWH and VKAs are both acceptable options and safe with breastfeeding. If VKAs are used postpartum, then bridging with LMWH is needed, especially in scenarios of higher thrombotic risk or protein C or S deficiency. DOACs do cross into breastmilk and should not be used with breastfeeding. However, if a patient is not breastfeeding then DOACs are an option. DOACs are associated with increased heavy menstrual bleeding (HMB) in the nonpregnant population, however, how DOACs affect lochia volume or duration post delivery is not known. Low-dose aspirin is safe with breastfeeding.

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Prevention of VTE in pregnancy

Given the limited data, clinical practice guidelines vary on recommendations for thromboprophylaxis in the setting of different thrombophilias and situational risk factors including postcesarean delivery. The American Society of Hematology (ASH) 2018 clinical practice guidelines recommends thromboprophylaxis with LMWH during pregnancy and for 6 weeks postpartum for patients with high-risk thrombophilia, and postpartum thromboprophylaxis alone for some of the mild thrombophilias (Table 3-4). For patients with a prior unprovoked or hormone-associated VTE, antepartum and 6 weeks of postpartum thromboprophylaxis is recommended. For patients with a prior VTE after a major provoking risk factor such as trauma or major surgery, then 6 weeks of postpartum thromboprophylaxis alone is recommended, along with antepartum clinical vigilance for symptoms of VTE or development of additional VTE risk factors. If the provoking risk factor that contributed to the initial VTE event was more minor (eg, long-haul travel or a minor procedure), or there are additional VTE risk factors during pregnancy, then a careful discussion that considers patient values and preferences is needed.

Recommendations

Please see Table 3-4 that highlights the 2018 ASH recommendations for prevention of VTE in pregnancy in patients with inherited thrombophilia and prior VTE.

Table 3-4 2018 ASH guideline recommendations for venous thromboembolism (VTE) prophylaxis in pregnancy

Condition	Antepaartum	Postpartum
Prior VTE that was unprovoked or associated with a hormonal risk factor	Recommends antepartum anticoagulant prophylaxis	Recommends postpartum anticoagulant prophylaxis
Prior VTE associated with a nonhormonal temporary provoking risk factor and no other risk factors	Suggests *against* antepartum anticoagulant prophylaxis	Recommends postpartum anticoagulant prophylaxis
Heterozygosity for factor V Leiden or prothrombin gene mutation	Without a family history: Suggests *against* thromboprophylaxis With a family history: Suggests *against* thromboprophylaxis	Without a family history: Suggests *against* antithrombotic prophylaxis With a family history: Suggests *against* antithrombotic prophylaxis
Protein C deficiency	Without a family history: Suggests *against* thromboprophylaxis With a family history: Suggests *against* thromboprophylaxis	Without a family history: Suggests *against* antithrombotic prophylaxis With a family history: Suggests postpartum antithrombotic prophylaxis
Protein S deficiency	Without a family history: Suggests *against* thromboprophylaxis With a family history: Suggests *against* thromboprophylaxis	Without a family history: Suggests *against* antithrombotic prophylaxis With a family history: Suggests postpartum antithrombotic prophylaxis
Compound heterozygosity	Without a family history: Suggests antepartum antithrombotic prophylaxis With a family history: Suggests antepartum antithrombotic prophylaxis	Without a family history: Suggests postpartum antithrombotic prophylaxis With a family history: Suggests postpartum antithrombotic prophylaxis
Homozygous factor V Leiden	Without a family history: Suggests antepartum antithrombotic prophylaxis With a family history: Suggests antepartum antithrombotic prophylaxis	Without a family history: Suggests postpartum antithrombotic prophylaxis With a family history: Suggests postpartum antithrombotic prophylaxis
Homozygous prothrombin gene mutation	Without a family history: Suggests *against* antithrombotic prophylaxis With a family history: Unable to make a recommendation (panelists favored prophylaxis)	Without a family history: Suggests postpartum antithrombotic prophylaxis With a family history: Suggests postpartum antithrombotic prophylaxis
Antithrombin deficiency	Without a family history: Suggests *against* thromboprophylaxis With a family history: Suggests antepartum antithrombotic prophylaxis	Without a family history: Suggests *against* thromboprophylaxis With a family history: Recommends postpartum antithrombotic prophylaxis
No or 1 clinical risk factor (excluding known thrombophilia or history of VTE)	Suggests *against* antepartum prophylaxis	Suggests *against* postpartum prophylaxis

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Management of VTE in pregnancy

Therapeutic-dose LMWH is recommended for the treatment of DVT and PE in pregnancy, with either once or twice daily LMWH dosing regimens being acceptable options. The duration of anticoagulation should include a minimum total duration of 3 months and also include the 6-week postpartum period. Systemic or catheter-directed thrombolysis should be reserved for limb or life-threatening VTE. The role of anti-Xa level monitoring is controversial and practice variation exists. The ASH 2018 guidelines for VTE in pregnancy *suggests against* anti-Xa level monitoring for VTE management, based on limited available data, absence of a validated anti-Xa range in pregnancy, and the added burden and cost of monitoring. There may be a role for anti-Xa level monitoring in selective higher-risk VTE cases, including in those with renal dysfunction or extremes of body weight.

Therapeutic-dose LMWH should be discontinued at least 24 hours, and prophylactic-dose LMWH (eg, enoxaparin [40 mg]) should be discontinued at least 12 hours, before neuraxial anesthesia is given the concern is for the rare but serious complication of spinal epidural hematoma. A timed delivery such as with an induction of labor is generally recommended for patients on therapeutic-dose LMWH to minimize postpartum hemorrhage and increased access to neuraxial anesthesia. There is more practice variation for patients on prophylactic-dose LMWH, with options that include holding LMWH dose at the onset of spontaneous labor, or a timed induction of labor. The 2018 ASH guidelines "suggest against a scheduled delivery with discontinuation of prophylactic anticoagulation compared with allowing spontaneous labor," but acknowledge the importance of patient values and preferences during decision-making. The use of intravenous UFH and/or inferior vena cava (IVC) filter placement should be limited to higher risk patients who have had a VTE close to delivery (eg, <2-4 weeks), especially given the technical challenges of IVC insertion in pregnancy because of the gravid uterus and IVC dilatation.

Postpartum, early resumption of therapeutic-dose anticoagulation has been shown to be associated with a higher bleeding risk. If an epidural is in place, then prophylactic-dose LMWH should be restarted 12 hours after needle/catheter placement and therapeutic-dose LMWH restarted 24 hours after needle/catheter placement, and 4 hours after catheter removal. The authors consider resuming a prophylactic-dose LMWH postpartum prior to escalating to therapeutic-dose LMWH, but this decision varies according to VTE acuity, bleeding risk, and institutional practices. In the event that LMWH or UFH is held, sequential pneumatic compression devices should be used.

Recommendations

Treatment with either once or twice daily LMWH regimens is recommended for treatment of a new VTE in pregnancy. Anti-X level monitoring are not recommended in the 2018 ASH guidelines but may be used in select high-risk VTE cases, especially in the first month of therapy, such as in patients with renal dysfunction or obesity. For patients on therapeutic-dose LMWH, a planned delivery with an induction of labor is recommended so anticoagulation can be held for at least 24 hours to minimize bleeding and allow access to neuraxial anesthesia. If the VTE event is closer to delivery (<2-4 weeks), then careful planning with a multidisciplinary team is needed.

Management of superficial vein thrombosis

The 2018 ASH guidelines for management of venous thromboembolism in the context of pregnancy suggests the use of LMWH for treatment of superficial vein thrombosis in pregnancy, compared to no anticoagulant therapy. Practice variation exists on the dose and duration of LMWH, with a common duration being at least 6 weeks of LMWH to minimize the risk of recurrence and progression to a DVT. The dose and duration should be based on extent of superficial vein thrombosis, location to the deep vein system (eg, proximity to the saphenofemoral junction) and if other VTE risk factors are present. Nonanticoagulant options including warm or cool compresses and compression stockings may improve symptoms, including in patients with symptomatic varicose veins. Nonsteroidal anti-inflammatory drugs are not recommended in pregnancy.

Management of ovarian vein thrombosis

Symptomatic ovarian vein thrombosis (OVT) is a relatively uncommon event, complicating approximately 1 per 600, to 1 per 2000 pregnancies, and is most often in the postpartum period and associated with cesarean delivery. Symptomatic OVT typically presents with fever and lower abdominal pain within the weeks following delivery. Complications of symptomatic OVT include sepsis, thrombus extension (25% to 30%) to the inferior vena cava or left renal vein, or (rarely) pulmonary embolism. Asymptomatic OVT (with a 30% incidence of pelvic vein thrombosis reported on screening MRI following vaginal delivery and 46% incidence of pelvic vein thrombosis on screening MRI following cesarean delivery) is more common and is likely benign. Management guidelines are limited by a paucity of studies in the literature. Anticoagulation is indicated for patients with symptomatic or extensive postpartum OVT, and antibiotics

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should be used adjunctively when infection is suspected. Asymptomatic OVT in the postpartum period and in the general population usually does not require treatment. The duration of anticoagulation varies but is most commonly given for 3 months.

Management of heparin-induced skin reactions

Skin reactions, varying from type 1 urticarial eruptions to type IV delayed hypersensitivity reactions, have been reported in 0.3% to 0.6% of patients receiving heparin. However, in at least one prospective study of 66 pregnant women, 29% reported pruritus, local erythema, and (less commonly) subcutaneous infiltrates and pain at the injection site. In pregnant women without signs of a type I reaction, switching to another LMWH preparation is recommended. In approximately one-third in whom a skin reaction recurs after switching from one LMWH preparation to another, switching to fondaparinux is recommended.

Management of HIT in pregnancy

In pregnant patients with confirmed HIT, danaparoid does not cross the placenta and is considered to be the first-line therapy for treatment of HIT if it is available. Danaparoid is not available in the United States (Table 3-3). If danaparoid is not available, then fondaparinux is recommended. There is limited safety data in first trimester. Although fondaparinux crosses the placenta, the umbilical anti-Xa levels measured in the fetus are at one-tenth the maternal level. Similar to LMWH, fondaparinux has low oral bioavailability and appears to be safe with breastfeeding but limited data exists.

Thrombophilia and placenta-mediated pregnancy complications: what the hematologist needs to know

- Testing for antiphospholipid antibodies is recommended for patients with recurrent pregnancy loss, but other testing for inherited thrombophilia is *not* recommended.
- In patients with antiphospholipid syndrome (APS) and prior pregnancy loss that meets the revised Sapporo criteria, use of LMWH and aspirin is recommended to prevent recurrent pregnancy loss.
- There is no role for LMWH to prevent pregnancy loss or other adverse pregnancy outcomes for patients with inherited thrombophilia outside of a clinical trial.

Inherited thrombophilia and pregnancy complications

The association between inherited thrombophilia and pregnancy loss and other placenta-mediated pregnancy complications was first identified in several case-control studies of women with inherited thrombophilia. Over time, this association has not been consistently confirmed in methodologically stronger cohort studies. In a meta-analysis of cohort studies, only a modest association between heterozygous factor V Leiden and pregnancy loss remains. As for the role of LMWH in the prevention of recurrent pregnancy loss in patients with inherited thrombophilia, a randomized trial (the Thrombophilia in Pregnancy Prophylaxis Study [TIPPS] trial) showed lack of benefit with antepartum LMWH in pregnant women with thrombophilia and previous placenta-mediated pregnancy complications. This same finding of no benefit was confirmed in a subsequent meta-analysis of 8 randomized trials of LMWH versus no LMWH to prevent placenta-mediated pregnancy complications, including a subgroup of thrombophilia patients.

Recommendations

For women with a history of pregnancy loss or complications, screening for inherited thrombophilia is not recommended and LMWH is not recommended on the basis of this alone.

Antiphospholipid syndrome and pregnancy complications

The strongest evidence of an association between thrombophilia and pregnancy loss comes from studies in patients with antiphospholipid antibodies (aPLs). A diagnosis of APS requires at least one clinical criterion and one laboratory criterion based on the revised Sapporo criteria list that follows. The clinical criteria require either of the following:

1. Vascular thrombosis: 1 or more clinical episodes of arterial, venous, or small vessel thrombosis, or
2. Pregnancy morbidity:
   a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus; or
   b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of
      i) eclampsia or severe preeclampsia defined according to standard definitions; or
      ii) recognized features of placental insufficiency; or
   c) 3 or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

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The laboratory criteria require the presence of lupus anticoagulant or moderate-to-high titer antibodies to immunoglobulin G (IgG) or immunoglobulin M (IgM) anticardiolipin (>40 a microgram of IgG antibody or a microgram of IgM antibody or greater than the 99th percentile); or IgG or IgM beta-2-glycoprotein I (greater than the 99th percentile) on 2 occasions at least 12 weeks apart.

Among women with recurrent pregnancy loss (greater than or equal to 3 early losses <10 weeks of gestation), 15% have antiphospholipid antibodies. There is an increased proportion of aPL-positive patients who experience pregnancy loss after the 10th week of gestation. Antiphospholipid antibody screening is recommended in women with recurrent pregnancy loss (greater than or equal to 3 losses before 10 weeks, or 1 late loss at 10 weeks or greater). Correlation of positive aPLs with other placenta-mediated pregnancy complications such as fetal growth restriction (small for gestational age infant), preeclampsia, or placental abruption is more controversial. Several randomized studies, none of which were placebo controlled, have examined the effect of treatment of women with aPLs with aspirin, heparin, or both. These studies, which have been small and with heterogeneous criteria, generally have demonstrated an advantage of heparin and aspirin versus aspirin alone. However, more recent trials evaluating LMWH/aspirin versus aspirin alone did not show a difference in live birth rates. Guidelines generally recommend use of prophylactic-dose LMWH and aspirin to prevent recurrent pregnancy loss among patients who meet the revised Sapporo criteria with a history of 3 or more early pregnancy losses, or 1 or more late loss ≥10 weeks of gestation. There is less evidence and more guideline variation for those that do not meet the revised Sapporo criteria, or they have other placenta-mediated pregnancy complications. For patients with APS and prior thrombosis, therapeutic doses of LMWH are used often in combination with aspirin.

Recommendations

aPL screening is recommended in women with recurrent pregnancy loss (3 or more losses before 10 weeks, or 1 loss at 10 weeks or greater). For women with persistently positive aPL and pregnancy loss based on the revised Sapporo criteria, antepartum prophylactic LMWH and low-dose aspirin is recommended. For women with prior thrombotic events, therapeutic-dose LMWH is recommended, often in combination with low-dose aspirin.

Assisted reproductive technology

In women who undergo assisted reproductive technology, the risk of thrombosis is increased in both successful and unsuccessful cycles. Studies using the Swedish medical birth register have found that in successful pregnancies, women who undergo in vitro fertilization have an increased risk of VTE during pregnancy of 4- to 5-fold as compared to spontaneous conceptions, particularly during the first trimester. The risk of VTE is 100-fold if ovarian hyperstimulation syndrome develops (OHSS). OHSS, which develops in 1% to 5% of ART cycles, results from the injection of human chorionic gonadotropin which is used to finalize oocyte maturation and/or trigger oocyte release. OHSS results in arteriolar vasodilation, increased capillary permeability, shifts from the intravascular to the extravascular compartment, hyponatremia and hemoconcentration. In severe cases of OHSS, women can develop thromboembolism. OHSS is present in 90% of the arterial events associated with ART (at a median of 11 days post embryo transfer), and in approximately 80% of the venous events associated with ART (at a median of 42 days post embryo transfer).

The 2018 ASH guidelines for management of venous thromboembolism in the context of pregnancy suggest prophylactic LMWH in severe OHSS. LMWH anticoagulation can be withheld for 12 to 24 hours before oocyte retrieval, then resumed 6 to 12 hours after retrieval and continued for 3 months. LMWH is not recommended for routine ART without OHSS. There is little data on the role of thromboprophylaxis for patients with inherited thrombophilia or prior VTE. Based on expert opinion, thromboprophylaxis can be considered for those that would have also received antepartum thromboprophylaxis (eg, a high-risk thrombophilia or prior VTE). It is less clear on the management of patient with low-risk thrombophilias, but may be considered in nonsevere OHSS or if they would have received postpartum thromboprophylaxis based on guidelines after a careful discussion about the risks and benefits.

Recommendations

Prophylactic LMWH is suggested in severe OHSS and can be considered in those without OHSS but with high-risk thrombophilias or prior VTE. There is a lack of data for other scenarios (eg, low-risk thrombophilia) and a discussion about risks and benefits and patients' values and preferences is needed.

Management of mechanical heart valves

Without anticoagulant therapy, patients with mechanical heart valves have a high risk of arterial thromboembolism. Warfarin appears to be more effective than heparin in preventing valvular thrombosis in these patients but carries the highest rate of fetal complications. There is practice variation on the approach to anticoagulation, including continuing

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warfarin throughout pregnancy (especially if doses are ≤5 mg/day, international normalized ratio [INR] 2.5 to 3.5), sequential therapy with a combination of therapeutic LMWH up to 12 to 14 weeks of gestation and then warfarin or therapeutic LMWH throughout pregnancy. In a systemic review of 46 studies and 2468 pregnancies, the risk of maternal thromboembolic events was 2.7% (95% confidence interval [CI], 1.4 to 4.0) with VKA (INR 2.5 to 3.5) throughout pregnancy, 8.7% (95% CI, 3.9% to 13.4%) with LMWH throughout pregnancy, and 5.8% (95% CI, 3.8% to 7.7%) with sequential therapy; anticoagulation-related fetal/neonatal adverse events was 2% (95% CI, 0.3% to 3.7%), 0% and 1.4% (95% CI, 0.3% to 2.5%), respectively, per group. Some thromboembolic events may be caused by subtherapeutic LWMH dosing, lack of anti-Xa level monitoring, or poor patient compliance. The use of a concomitant antiplatelet is common and depends on valve location, type, and age of the replacement. Involvement of a cardiologist as part of the multidisciplinary team should be considered when making anticoagulation and antiplatelet decisions. Further guidance may be obtained from guidelines that have been published by the European Society of Cardiology 2018, American Heart Association 2014, and American College of Chest Physicians 2012.

Hematologic health issues in nonpregnant women

Heavy menstrual bleeding in the premenopausal woman: what the hematologist needs to know

- HMB can lead to anemia.
- Besides diagnosing and treating anemia (see Chapter 6) the hematologist should look for an abnormality of coagulation.
- Approximately 20% of all HMB is associated with an abnormality of coagulation.
- Approximately 80 to 90% of women with an underlying bleeding disorder and 70% on anticoagulation experience HMB.
- The patient who screens positive for an underlying bleeding disorder or is referred because of suspicion of a bleeding disorder should be thoroughly evaluated.
- In treating HMB, the hematologist will partner with a reproductive health care provider who will prescribe hormonal or possibly surgical therapy, while the hematologist will prescribe specific or nonspecific hemostatic therapy.

Definition, estimation, and causes of HMB

HMB is defined as greater than 80 mL of blood per cycle. The gold standard for the measurement of blood in sanitary products is the extraction of hematin, which is not feasible in clinical practice. However, in a rigorous study in which this method was used to measure menstrual blood loss, HMB was predicted on the basis of clots of ≥1 in. diameter, low ferritin, and "flooding," defined as a change of pad or tampon more often than hourly. When attempting to ascertain if a patient has HMB, these are signs and symptoms that can be queried.

Besides these signs and symptoms, a more objective measure of HMB is the pictorial blood assessment chart. To complete the chart, women compare both the degree of saturation of pads and tampons with those depicted on a chart (Figure 3-4). A total score of >100 per menstrual cycle is associated with menstrual blood loss of >80 mL (definition of HMB). A major limitation of this tool is that it must be completed prospectively, so results are not available at the time of initial evaluation. Completion of the score after the initial evaluation may be helpful in monitoring response to therapy.

In 2007, the International Federation of Gynecology and Obstetrics developed a useful construct in classifying HMB in terms of the acronym PALM-COEIN

Figure 3-4 Pictorial chart assessment of menstrual flow. A total score of >100 points (pts) is consistent with menorrhagia (80% sensitivity and specificity); >185 has >85% positive predictive value and positive predictive value. Adapted from Janssen CA et al, A simple visual assessment technique to discriminate between menorrhagia and normal menstrual blood loss, *Obstet Gynecol.* 1995;85(6):977-982 (© 1995 by The American College of Obstetricians and Gynecologists; https://journals.lww.com/greenjournal/pages/default.aspx), with permission.

The numbers 1-8 represent the consecutive days of your menstrual period. Please record, for each day, the number of pads you used that match each illustration

Pad	1	2	3	4	5	6	7	8
1 pt/pad								
5 pts/pad								
20 pts/pad								
Clots (Yes/No)								

The numbers 1-8 represent the consecutive days of your menstrual period. Please record, for each day, the number of tampons you used that match each illustration

Tampon	1	2	3	4	5	6	7	8
1 pt/tampon								
5 pts/tampon								
10 pts/tampon								
Clots (Yes/No)								

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(polyps, adenomyosis, leiomyoma [fibroids], malignancy and hyperplasia; coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified).

Screening for and evaluation of HMB

The patient referred for suspicion of a bleeding disorder or who screens positive for an underlying bleeding disorder with a validated bleeding score should be thoroughly evaluated by the hematologist. Even in the presence of gynecologic disease, such as ovulatory dysfunction in adolescence or uterine pathology in the perimenopause, a disorder of coagulation may be an additional contributing factor to HMB and should be considered. A screening tool developed by Philipp et al. for use in women with HMB may identify women who are more likely to have an underlying bleeding disorder. The tool contains 8 questions in 4 categories: (1) severity of HMB, (2) family history of bleeding disorder, (3) personal history of excessive bleeding, and (4) history of treatment for anemia (Table 3-5). The screen is considered positive if an affirmative response is obtained in any 1 of the 4 categories. The sensitivity of this tool for underlying hemostatic defects in adult women was 89%, which increased to 93% to 95% with the addition of a serum ferritin level of ≤20 ng/mL and a pictorial blood assessment chart score of >185, respectively. A PFA-100® (Tarrytown, NY, USA) did not increase the sensitivity of the screening tool for all bleeding disorders but did increase the sensitivity for VWD to 92%.

Table 3-5 Screening tool for inherited bleeding disorders in women presenting with heavy menstrual bleeding

Screening questions	Score
Q1. How many days did your period usually last, from the time bleeding began until it completely stopped?	1 = ≥7 days 0 = <7 days
Q2. How often did you experience a sensation of "flooding" or "gushing" during your period?	1 = Every or most periods 0 = Never, rarely, or some periods
Q3. During your period did you ever have bleeding where you would bleed through a tampon or napkin in ≤2 hours?	1 = Every or most periods 0 = Never, rarely, or some periods
Q4. Have you ever been treated for anemia?	1 = Yes 0 = No
Q5. Has anyone in your family ever been diagnosed with a bleeding disorder?	1 = Yes 0 = No
Q6. Have you ever had a tooth extracted or had dental surgery?	1 = Yes, if had and bled 0 = No
Q7. Have you ever had surgery other than dental surgery? Q7a. Did you have bleeding problem after surgery?	See 7a. below 1 = Yes 0 = No
Q8. Have you ever been pregnant? Q8a. Have you ever had a bleeding problem after delivery or after a miscarriage?	See 8a. below 1 = Yes 0 = No

Scores are adapted from Philipp CS et al, *Am J Obstet Gynecol.* 2011;204:209.e1-209.e7; and Philipp CS et al, *Am J Obstet Gynecol.* 2008;198:163.e1-163.e38.

The patient's evaluation will include a review of the history (menstrual, medical, bleeding, medications), a review of the gynecologic evaluation and a laboratory assessment for an underlying bleeding disorder. In a meeting of experts in the fields of hematology and obstetrics and gynecology, a consensus was achieved on what should comprise the laboratory assessment for an underlying bleeding disorder. Evaluation should include the following:

- Complete blood count
- Ferritin (if not performed already)
- Activated partial thromboplastin time
- Prothrombin time (PT) and INR
- VWF (measured with ristocetin cofactor activity and antigen)
- Factor VIII (FVIII)
- Fibrinogen

While testing appears to be most sensitive during menstruation when coagulation factor levels, most notably VWF and FVIII, are potentially at their lowest, testing should not be delayed to coincide with menstruation nor should hormonal be discontinued. Nonetheless, women with mild type 1 VWD may have normal results when combined hormonal contraceptives are used. If the preceding tests are normal, studies of platelet aggregation and platelet release should be considered. Hematologic assessments should be repeated as necessary to confirm the diagnosis of a bleeding disorder.

For the patient on anticoagulation or antiplatelet medication, the evaluation will also include an assessment as to whether antiplatelet medication or anticoagulation can be safely reduced or discontinued. A creatinine is recommended in the evaluation of the patient on a direct oral anticoagulant.

Hormonal treatment of HMB

Not only will the treatment strategy depend on whether there is ovulatory dysfunction, uterine pathology, or an abnormality of coagulation, the treatment strategy will also depend on the age of the patient and her desire for immediate or long-term fertility. In a woman who desires future fertility, who is not trying to conceive, and who does not have contraindications to estrogen, first-line

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therapies are hormonal contraceptives, which are highly effective in reducing menstrual blood flow. Combined hormonal contraceptives containing an estrogen (usually ethinyl estradiol), and a progestin (a synthetic progestogen) suppress ovulation (and also prevent hemorrhagic ovarian cysts), regulate the menstrual cycle, and reduce menstrual blood flow. Combined hormonal contraceptives are available in the form of oral contraceptive pills (taken daily), patches (changed weekly), and vaginal rings (changed monthly). Progestin-only contraceptives are an alternative to combined hormonal contraceptives. Progestin-only contraceptives are available in the form of pills (taken daily), intramuscular or subcutaneous injections (administered every 3 months), subcutaneous implants (changed every 3 years), and the levonorgestrel intrauterine device (IUD) (changed every 3 or 5 years depending on the size). An advantage of the levonorgestrel IUD is that there is very little systemic absorption of the progestin. A disadvantage of the levonorgestrel IUD, however, is that it does not suppress ovulation and does not suppress formation of hemorrhagic ovarian cysts (half of which occur in the setting of an underlying bleeding disorder or anticoagulation). Progestin-only pills only partially suppress ovulation.

In women with a history of thrombosis who are on anticoagulation, data from the EINSTEIN DVT and PE anticoagulation trial found that women who used combined hormonal contraceptives (with a recurrence rate of VTE of 3.7%) were no more likely to suffer recurrent VTE than were women who used progestin-only contraceptives (with a recurrence rate of 3.8% per year) or women who did not use any hormonal contraceptives (recurrence rate 4.7% per year).

In women with a history of thrombosis who are not on anticoagulation there has generally been agreement that they should not receive combined hormonal contraceptives to help manage their HMB. There is new evidence that the injectable contraceptive, depot medroxyprogesterone (DMPA), also increases the risk of thrombosis, although other lower-dose progestin-only contraceptives (pills, subcutaneous implants, and the levonorgestrel IUD) do not.

Sometimes women with HMB are treated with non-contraceptive progestin formulations, such as medroxyprogesterone or norethindrone, which generally contain higher doses than those used for contraception and which may increase the risk of VTE. There are limited data on the increased risk of VTE when progestins are used for the treatment of abnormal uterine bleeding (presumably in higher doses) as opposed to when progestins are used for contraception, but one nested case-control study found an adjusted OR of 5.3, 95% CI 1.5 to 18.7. The formulation of the progestin(s) in this study was not specified.

Hemostatic treatment of HMB

In women who have failed hormonal therapy and desire to preserve fertility, hemostatic therapy is the next step in treatment. For women who are trying to conceive and therefore cannot use hormonal therapy, it is the preferred treatment. Hemostatic therapy may be specific to a particular disorder or nonspecific, as is the case with the antifibrinolytic medication, tranexamic acid. In the 4 randomized controlled trials (RCTs) that used tranexamic acid, tranexamic acid was administered in doses of 1.0 g 4 times per day or 1.3 g 3 times per day for a total of 3.9 to 4.0 g per day for up to 5 days of the menstrual cycle. There are no studies on the safety of tranexamic acid in women with a history of thrombosis and there are no studies of the safety of tranexamic acid as an adjunct to hormonal therapy. Multiple studies, however, have demonstrated no increased risk of VTE with the use of tranexamic acid, although studies have excluded women with a history of thrombosis or those using hormonal contraception.

Desmopressin is considered specific therapy for type 1 VWD and factor VIII deficiency, but it has also been used as nonspecific hemostatic therapy. The dosing of desmopressin for the treatment of HMB is 300 μg administered on days 2 and 3 of the menstrual cycle (1 puff in each nostril each day). In a randomized crossover study of intranasal desmopressin versus placebo, desmopressin was more effective. In another randomized crossover study of tranexamic acid versus intranasal desmopressin, tranexamic acid was more effective than desmopressin.

A number of single plasma-derived or recombinant coagulation factors as well as 3 and 4 factor prothrombin complex concentrates (PCCs) are available to treat specific coagulation factor defects. VWD is the most common inherited bleeding disorder, accounting for 90% of women seen at CDC-designated hemophilia treatment centers, and is the condition for which women with HMB are most likely to receive specific hemostatic therapy.

Surgical treatment of HMB

For women who have completed childbearing, surgical management of HMB is an option. Dilation of the cervix and curettage (scraping) of the uterus (D & C) is only temporarily effective and may cause more bleeding. Endometrial ablation (destruction of the uterine lining) is highly effective, but unfortunately 8.5% of women require further surgery. Uterine artery embolization has not been studied except in women with fibroids. Hysterectomy is the definitive treatment for HMB but is associated with the complications of major surgery. Nonetheless, in a randomized trial of hysterectomy versus medical therapy for abnormal uterine bleeding, hysterectomy was superior to

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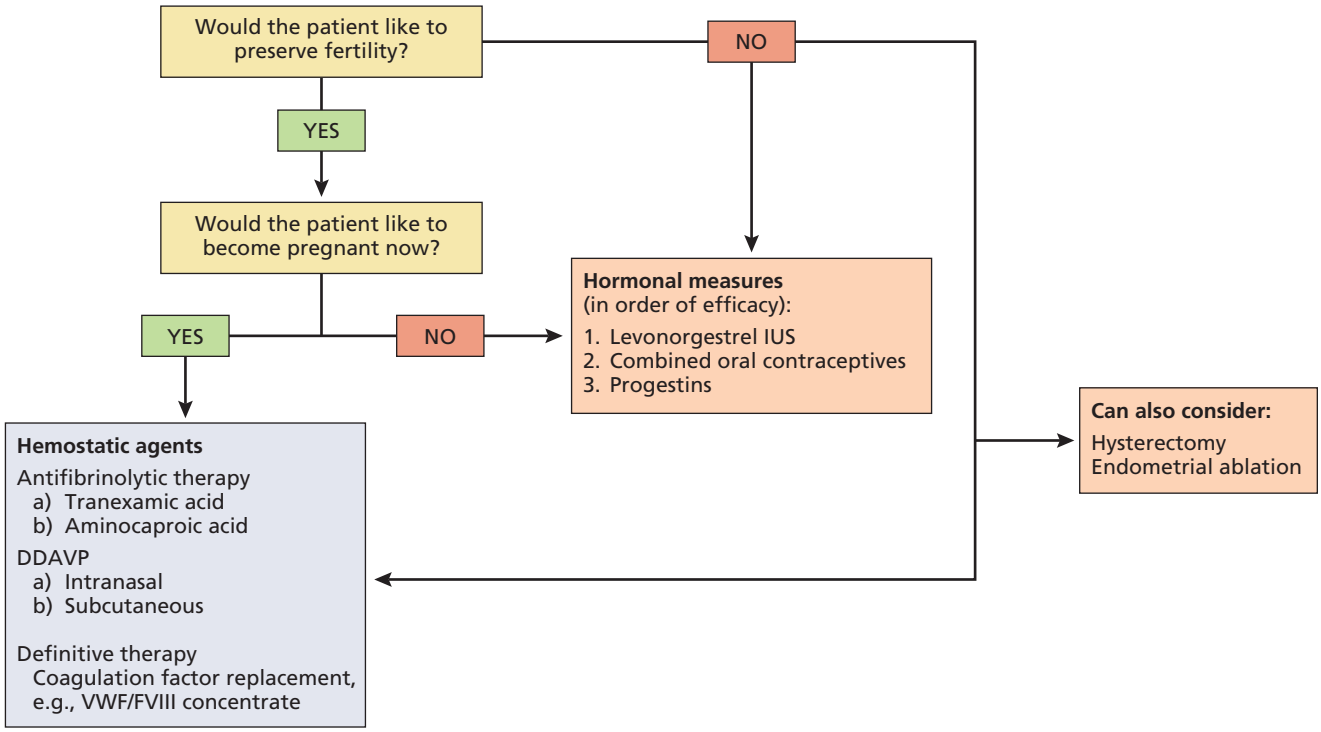

Figure 3-5 Suggested algorithm for management of bleeding disorder–related HMB. DDAVP, 1-desamino-8D-arginine vasopressin**;** IUS, intrauterine system or intrauterine device; VWF, von Willebrand factor. Adapted from James AH et al, *Am J Obstet Gynecol*. 2009;201:12e1-12e8, with permission.

medical treatment for improving health-related quality of life. See Figure 3-5 for a suggested algorithm for management of bleeding disorder–related HMB.

Recommendations

The patient who screens positive for an underlying bleeding disorder or is referred for suspicion of a bleeding disorder should be thoroughly evaluated. In treating HMB, the hematologist will partner with a reproductive health care provider who will prescribe hormonal or possibly surgical therapy, while the hematologist will prescribe specific or nonspecific hemostatic therapy.

Thrombosis and exogenous hormones: what the hematologist needs to know

- Exogenous hormones may increase the risk of thrombosis.
- Those at high risk of thrombosis should be counseled against the use of exogenous hormones or should receive anticoagulation.

Hormonal contraceptives

Combined hormonal contraceptives (CHCs) contain both an estrogen and a synthetic progestogen (progestin) and are associated with an increased risk of both arterial and venous thrombosis. Estrogen increases procoagulants, such as factor VIII, VWF, and fibrinogen, and decreases fibrinolytic activity and the natural anticoagulant protein S. Acquired resistance to activated protein C can develop, partly because of the decrease in protein S. Nonetheless, the mechanism or mechanisms by which estrogen increases the risk of thrombosis are not completely understood. Despite the increased risk of thrombosis, the most common method of contraception in the United States today is birth control pills. The risk of VTE with CHCs has been variously reported depending on the study, the dose of estrogen and type of progestin. Women using CHCs have a 2- to 6-fold increased risk of VTE compared to women not using CHCs. Reports of the absolute risk of VTE range from 10 to 60 per 100,000 women-years for women using combined hormonal contraceptive pills, to 40 to 100 per 100,000 women-years for women using combined hormonal contraceptive patches, to 80 per 100,000 women-years for women using the combined contraceptive vaginal ring. These absolute risks are compared to a background risk of VTE of 20 to 40 per 100,000 women-years in women using no hormonal contraceptives and a background risk of 200 per 100,000 women-years in women who are pregnant.

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Although the component of CHCs most closely associated with an increased risk of thrombosis is estrogen, progestins, depending on their formulation or their dosage, may further increase the risk. The progestins desogestrel, drospirenone, and cyproterone acetate (not available in the United States) further increase the risk compared to levonorgestrel for a given dose of estrogen. There is new evidence that the injectable contraceptive DMPA also increases the risk of thrombosis approximately 2- to 3-fold, although lower-dose progestin-only contraceptives (pills, subcutaneous implants, and the levonorgestrel IUD) do not.

Some of the risk factors for thrombosis to be considered before prescribing hormonal contraceptives and their relative risks are listed in Table 3-6. Thrombophilia, smoking, and obesity have been shown to act synergistically with hormonal contraceptives to increase the risk of thrombosis. Other risk factors may act synergistically as well.

Women with a history of thrombosis who are on long-term anticoagulation and who use CHCs are no more likely to suffer recurrent VTE than women who use progestin-only contraceptives or women who do not use any hormonal contraceptives. Therefore, with rare exception, women who experience a thrombotic event and will be anticoagulated should not be counseled to avoid hormonal contraceptives. Women with a history of thrombosis who are not on long-term anticoagulation, however, should be counseled against using CHCs or DMPA. Lower-dose progestin-only contraceptives (pills, subcutaneous implants and the IUD) do not increase the risk of thrombosis and are safe.

Table 3-6 Relative risks of various risk factors for venous and arterial thromboembolism

Risk factor	Venous	Arterial
Surgery, trauma, immobilization	5-50	unknown
Overweight and obesity	2-3	1.5-2.0
Hypertension	0.7-1.3	1.5-2.0
Diabetes mellitus	0.7-2.0	2-3
Smoking	1.2-2.4	2.5-3.5
Dyslipidemia	0.8-1.5	2-3
Malignancy	7-20	unknown
Lupus anticoagulant	3-8	3-8
Rheumatoid arthritis	2-2.5	1.5-2.5
Systemic lupus erythematosus	3-8	3-8
Inflammatory bowel disease	3-4	1.0-2.0
Nephrotic syndrome	3-10	3-10
Inherited thrombophilia	2-20	1.1-7.0

Adapted from Lijfering WM et al, *Semin Thromb Hemost*. 2011;37(8):885-896, with permission. © Georg Thieme Verlag KG.

Menopausal hormone therapy

The primary role for menopausal hormone therapy (HT) is to relieve vasomotor symptoms (hot flashes, night sweats, and sleep disruption), prevent or reverse genitourinary symptoms (including vaginal atrophy), prevent bone loss and fractures, and improve quality-of-life issues such as depressed mood or sleep deprivation. For women who still have a uterus, menopausal HT typically consists of estrogen and a progestin. Estrogen without a progestin increases the risk of endometrial cancer. For women without a uterus, menopausal HT typically consists of estrogen alone.

While the mechanism or mechanisms by which estrogen increases the risk of thrombosis are not completely understood, both observational studies and RCTs have shown a 2- to 3-fold increased risk of VTE with oral menopausal HT, typically an estrogen and a progestin. Compared to estrogen with a progestin, the risk of VTE was lower with estrogen alone and not significantly elevated when compared to placebo. No large scale RCTs of oral estrogen versus transdermal estrogen versus placebo have been conducted, but observational studies suggest a decreased risk of VTE among women using transdermal estrogen compared to women using oral estrogen. Table 3-7 lists the relative risk of thrombosis associated with various estrogen formulations.

Women with a history of thrombosis who are on long-term anticoagulation and who use menopausal HT are unlikely to suffer recurrent VTE any more than women who do not use menopausal HT. Therefore, with rare exception, women who experience a thrombotic event and will be anticoagulated do not need to be counseled to discontinue menopausal HT. Women with a history of thrombosis who are not on long-term anticoagulation, however, should be counseled against using menopausal HT.

A frequent challenge facing clinicians who care for menopausal women with a history of thrombosis, or who

Table 3-7 List of the relative risk of thrombosis associated with various estrogen formulations

Relative thrombotic risk	Estrogen
High	Ethinylestradiol 50 μg
Intermediate	Ethinylestradiol 30-35 μg
Lower intermediate	Ethinylestradiol 20 μg
Moderately low	Conjugated equine estrogen
Low	Oral estradiol
	Estradiol valerate—parenteral
Very low	Transdermal estrogen

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are otherwise at high risk for thrombosis, is symptom management that does not include systemic estrogen, which is discouraged unless a woman is fully anticoagulated. For treatment of genitourinary symptoms, options include vaginal lubricants and moisturizers. If unsuccessful, low-dose vaginal estrogen or intravaginal dehydroepiandrosterone may be considered. There is minimal systemic absorption with these preparations, and no low-dose vaginal preparations have been shown to increase the risk of VTE. Multiple nonpharmacologic or nonhormonal therapies have been used to treat hot flashes and night sweats. While studies of other therapies have shown negative or mixed results, weight loss, cognitive behavioral therapy, and clinical hypnosis have been shown to be effective in RCTs. For more severe vasomotor symptoms, nonhormonal pharmacologic therapies that have been shown to be effective include several selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) along with gabapentin. If nonhormonal therapies are unsuccessful, low-dose transdermal estrogen could be considered.

Male-to-female hormone therapy

The medical care of transgender patients depends on the use of hormone therapy to develop and maintain the physical characteristics of the patient's gender identity. This involves regimens to suppress endogenous sex hormone production and maintain sex hormone levels in the physiologic range for the affirmed gender, including after gender-affirming surgeries. The essential hormone used to transition from male to female (transgender women) is estrogen. Forms of estrogen that are used include combined hormonal contraceptive pills (which contain the estrogen ethinyl estradiol) and menopausal hormone therapy (which contains the estrogen estradiol). Estrogen treatment alone, however, is insufficient to suppress testosterone production in transgender women. Medications used to suppress testosterone production are gonadotropin-releasing hormone agonists and cyproterone acetate (not available in the United States), which further increases the risk of VTE when combined with estrogen.

While the mechanism or mechanisms by which estrogen increases the risk of thrombosis are not completely understood, a meta-analysis estimated the crude incidence rate of VTE associated with estrogen use in transgender women to be 2.3 per 1000 patient-years (the approximate rate of thrombosis during pregnancy).

As opposed to the use of hormonal contraceptives, where alternatives exist for contraception, or the use of menopausal hormone therapy, where alternatives exist for the management of menopausal symptoms, there is no alternative to estrogen for the development and maintenance of female sex characteristics. Transgender women need to continue hormone therapy. Therefore, for transgender women with a history of thrombosis, anticoagulant therapy should also be prescribed.

Female-to-male hormone therapy

The essential hormone used to transition from female to male (transgender men) is testosterone. While an increase in red blood cell mass is expected, no increased risk of VTE has been observed in transgender men.

Recommendations

Women who are fully anticoagulated may continue the use of exogenous hormones. Women with a history of thrombosis, or who are otherwise at high risk of thrombosis, should be counseled to avoid combined hormonal contraceptives and depot medroxyprogesterone (DMPA), and should be counseled to avoid oral menopausal hormone therapy. Transgender women using male-to-female hormone therapy will need to continue this therapy and, therefore, will need anticoagulation.

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